Estimating the Instantaneous Asymptomatic Proportion With a Simple Approach: Exemplified With the Publicly Available COVID-19 Surveillance Data in Hong Kong

Chunyu Li [1†], Shi Zhao [2,3*†], Biao Tang [4,5], Yuchen Zhu [1], Jinjun Ran [6], Xiujun Li [1*‡] and Daihai He [7*‡]

[1] Department of Biostatistics, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, China, [2] JC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong, China, [3] Chinese University of Hong Kong (CUHK) Shenzhen Research Institute, Shenzhen, China, [4] School of Mathematics and Statistics, Xi'an Jiaotong University, Xi'an, China, [5] Laboratory for Industrial and Applied Mathematics, Department of Mathematics and Statistics, York University, Toronto, ON, Canada, [6] School of Public Health, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China, [7] Department of Applied Mathematics, Hong Kong Polytechnic University, Hong Kong, China

Background: The asymptomatic proportion is a critical epidemiological characteristic that modulates the pandemic potential of emerging respiratory virus, which may vary depending on the nature of the disease source, population characteristics, source–host interaction, and environmental factors.

Methods: We developed a simple likelihood-based framework to estimate the instantaneous asymptomatic proportion of infectious diseases. Taking the COVID-19 epidemics in Hong Kong as a case study, we applied the estimation framework to estimate the reported asymptomatic proportion (rAP) using the publicly available surveillance data. We divided the time series of daily cases into four stages of epidemics in Hong Kong by examining the persistency of the epidemic and compared the rAPs of imported cases and local cases at different stages.

Results: As of July 31, 2020, there were two intermittent epidemics in Hong Kong. The first one was dominated by imported cases, accounting for 63.2% of the total cases, and the second one was dominated by local cases, accounting for 86.5% of the total cases. The rAP was estimated at 23.1% (95% CI: 10.8–39.7%) from January 23 to July 31, and the rAPs were estimated at 22.6% (95% CI: 11.1–38.9%) among local cases and 38.7% (95% CI: 9.0–72.0%) among imported cases. Our results showed that the rAPs of local cases were not significantly different between the two epidemics, but increased gradually during the first epidemic period. In contrast, the rAPs of imported cases in the latter epidemic period were significantly higher than that in the previous epidemic period.

Conclusion: Hong Kong has a high rAP of imported COVID-19 cases and should continue to strengthen the detection and isolation of imported individuals to prevent the resurgence of the disease.

Keywords: COVID-19, likelihood-based framework, instantaneous asymptomatic proportion, Hong Kong, epidemic

INTRODUCTION

An atypical pneumonia case in early December 2019 caught the attention of medical institutions and was later confirmed to be novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1, 2]. Since early December 2019, the disease has spread rapidly around the world, with many countries and regions reporting an exponential increase in confirmed cases. In the face of tensions all over the world, the World Health Organization announced that the COVID-19 outbreak was considered as a Public Health Emergency of International Concern since January 31, and eventually classified it as a pandemic on March 11, 2020 [3]. As of August 16, 2020, 216 countries and territories had reported more than 21 million confirmed cases, including 760,000 deaths [4]. While these numbers are horrifying, they are only a fraction of those infected.

Most of the COVID-19 infections appear to have two outcomes, some become severely ill or even fatal (symptomatic infections), while others show no symptom (asymptomatic infections) [5]. In other words, asymptomatic infected individuals are defined as those who have positive RT-PCR testing outcome without any symptom. The asymptomatic COVID-19 infections have been frequently reported since January 2020 and take a large ratio of the total COVID-19 cases [6–8]. Several studies showed that the viral load of asymptomatic individuals is similar to that of symptomatic cases, which suggested that asymptomatic individuals can also promote the spread of the disease [9, 10]. In parallel, He et al. [11] showed that infectiveness of asymptomatic cases was 25% of that related to the symptomatic ones. Moreover, Day et al. [12] showed that the majority (from 50 to 75%) of people infected with COVID-19 were asymptomatic, but represented "*a formidable source*" of contagion. On the other hand, a previous study reported that asymptomatic individuals can still transmit the pathogen even 14 days later after they become infectious [5].

Based on these evidences mentioned above, we can see that it is fundamental to estimate the proportion of asymptomatic cases, further evaluate the impact of it on the disease burden and the effectiveness of the control interventions, and finally provide the decision-making basis in controlling the spread of the diseases [13–17]. At present, many studies have estimated the asymptomatic proportion of total COVID-19-infected cases at different sites by observational studies or mathematical models [18–25]. These estimated proportions were raw rates or assumed to remain constant over time. However, asymptomatic proportion may vary depending on the nature of the disease source, population characteristics (e.g., age structure, sex, health status, immune status, and genetic characteristics), pathogen–host interaction, and environmental factors. At the same time, in several countries or regions, the COVID-19 epidemics resurge and have a second wave of peak after a brief respite. It remains unknown whether the instantaneous asymptomatic proportion will change during this process [6].

The main purpose of this study is to develop a simple likelihood-based but generalized framework to estimate the instantaneous asymptomatic proportions for uncovering the features of COVID-19, thereby providing insights into understanding the spread of epidemics. Taking the epidemics in Hong Kong as a case study, we demonstrate the estimation framework by using the publicly available COVID-19 surveillance data.

METHODS

Estimation Framework

We denote the time interval between symptoms onset (if symptomatic) and being confirmed as τ, and let $f(\tau)$ be the probability distribution function (PDF) of τ. That is, if one case is reported on date t who becomes symptomatic eventually, the value of $f(\tau)$ is considered as the relative likelihood of symptoms onset on date $(t + \tau)$.

We assume that all symptomatic cases will be confirmed (most likely in Hong Kong), while confirmed cases can be symptomatic, pre-symptomatic, or asymptomatic at the time of reporting. Thus, the term τ need not necessarily be positive; i.e., negative values are also possible theoretically. Hence, we consider all the confirmed cases as the "pool" of symptomatic cases, and we model this candidate pool as a time-varying function denoted by $\Phi(t)$ on date t. On date t, the ith case, who is reported on date υ_i, contributes $f(\tau = \upsilon_i - t)$ to $\Phi(t)$. For the contribution from all reported cases, $\Phi(t)$ is summated as in Equation (1).

$$\Phi(t) = \sum_i f(\tau = \upsilon_i - t) \tag{1}$$

Hence, the reported asymptomatic proportion (rAP), i.e., the asymptomatic proportion among reported cases, on date t is calculated by $rAP_t = 1 - \alpha_t/\Phi_t$. Here, α_t is the observed number of cases with symptoms onset on date t, and Φ_t is the discretized $\Phi(t)$ on date t.

Given the infection time of one case (as condition), the onset time of this case is conditionally independent from each other case. Thus, to construct the likelihood profile, we model α_t as a binomial process with sizes at Φ_t (rounding to the closest integer) and successful probabilities at rAP_t to be estimated. As such, by fitting to the daily number of symptomatic cases time series, the rAP_t can be estimated by using the maximum likelihood estimation approach. The 95% confidence intervals (95% CI) of rAP_ts are calculated by using the profile likelihood estimation framework with a cutoff threshold determined by a Chi-square quantile [26], as well as previously adopted in [27–32].

COVID-19 Surveillance Data in Hong Kong

For demonstration, we used the publicly available COVID-19 surveillance data from January 23 to August 8, 2020 in Hong Kong as an example to construct the instantaneous rAP_ts series. The daily reported number of COVID-19 cases and date of onset were collected from https://www.coronavirus.gov.hk/eng/index.html. A laboratory-confirmed case was defined if the patient had a positive test of SARS-CoV-2 virus by the real-time reverse-transcription-polymerase-chain-reaction (RT-PCR) assay or high-throughput sequencing of nasal and pharyngeal

TABLE 1 | Summary of cases and the estimated asymptomatic proportions in the reported imported and local COVID-19 confirmed cases (rAP) at different stages of the epidemic in Hong Kong.

Stage	Period	# of cases			Daily cases	rAP	
		Total	Imported	Local		Imported	Local
(I)	Jan 23–Mar 7	110	32 (29.1%)	78 (70.9%)	2.4	51.9% (5.7–94.6%)	54.6% (2.3–99.1%)
(II)	Mar 8–Apr 3	753	476 (63.2%)	277 (36.8%)	27.9	27.3% (6.6–60.1%)	22.4% (2.6–64.1%)
(III)	Apr 4–Jun 30	343	287 (83.7%)	56 (16.3%)	3.9	68.0% (15.8–98.5%)	59.4% (9.9–98.8%)
(IV)	Jul 1–Jul 31	2,066	279 (13.5%)	1,787 (86.5%)	66.6	56.4% (13.2–91.6%)	22.2% (11.9–36.2%)
Pooled est.	Jan 23–Jul 31	3,272	1,074 (32.8%)	2,198 (67.2%)	17.1	38.7% (9.0–72.0%)	22.6% (11.1–38.9%)

The estimates are showed in "point estimate (95% CI)" format.

swab specimens (33). Only laboratory-confirmed cases were included in this study.

We divided the time series of daily cases in Hong Kong into different stages of the epidemic by examining the persistency of the epidemic. In this study, we considered the criterion that the epidemic persists with the daily number of cases larger than 5 for three consecutive days, but does not persist otherwise. Following this criterion, we have the following four stages of the epidemic, and they included:

- stage (I): from January 23 to March 7, with sporadic cases,
- stage (II): from March 8 to April 3, with an epidemic peak,
- stage (III): from April 4 to June 30, with sporadic cases, and
- stage (IV): from July 1 to July 31, with another epidemic peak.

Based on the estimated instantaneous asymptomatic proportion, we summarized the pooled asymptomatic proportions during the four different stages. To avoid the estimation inaccuracy due to reporting delay, we excluded the data from August 1 to August 8, 2020, and conducted the estimation using the remaining dataset.

To set up the initial conditions of the model framework in Equation (1), we initialized the PDF $f(\cdot)$ by a gamma distribution. Although τ can be negative theoretically, the situation when the report is prior to the symptoms onset rarely occurs in Hong Kong (only 1 out of a total of 3,067 symptomatic cases). Thus, for simplification, we model $f(\cdot)$ as PDF defined all positive values, which will not affect our main conclusions. We fitted gamma distribution $f(\cdot)$ to the observed time intervals between symptoms onset and being reported, and the parameters of $f(\cdot)$ are estimated by using the maximum likelihood estimation. We estimated the mean at 6.0, 7.2, or 5.7 days, and standard deviation (SD) at 4.3, 6.6, or 3.4 days for all, imported, or local COVID-19 cases, respectively. These estimates are implemented to set up $f(\cdot)$ in Equation (1) for further rAP estimation.
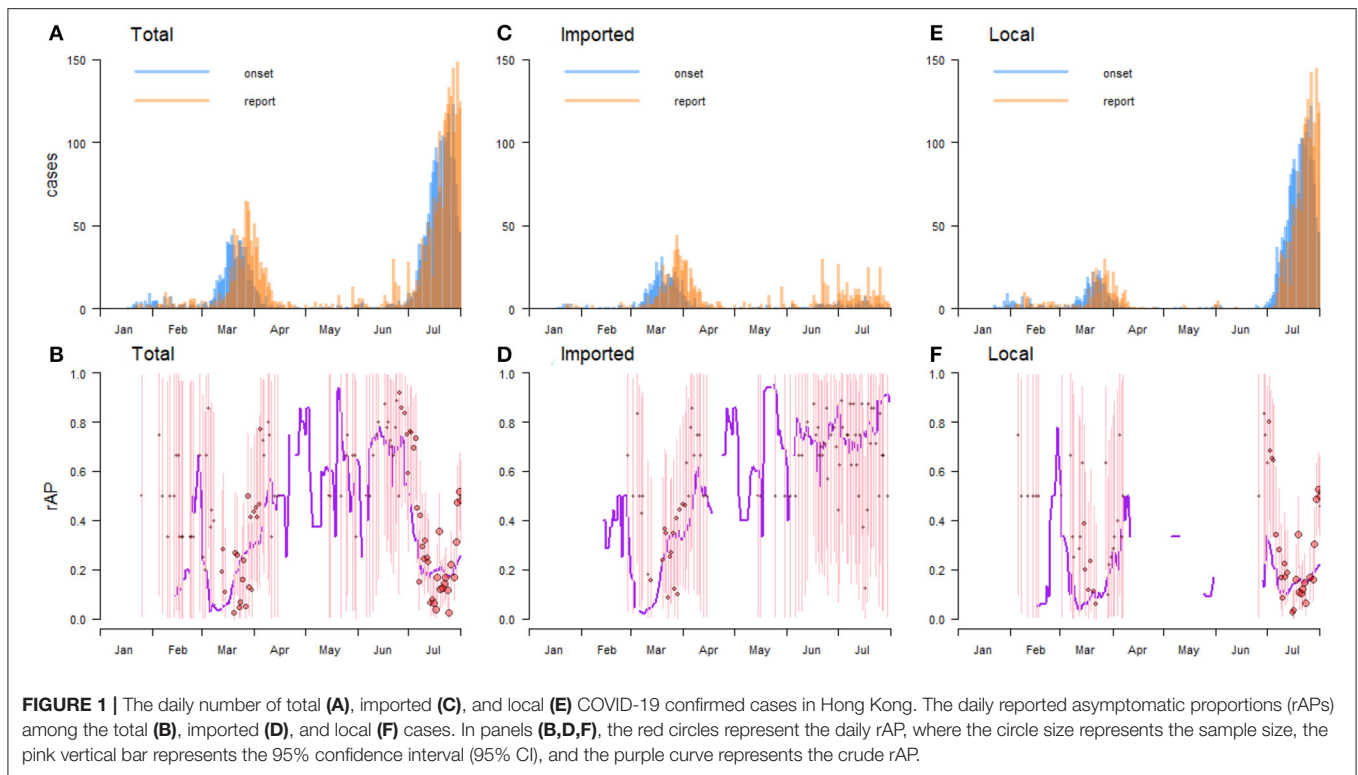
RESULTS

By July 31, a total of 3,272 cases were reported in Hong Kong, of which 67.2% were locals and 32.8% were imported, respectively. In particular, the first two cases were reported on January 23, 2020, and both were imported. In stage (I), all cases were imported in the first week, after which the local transmission emerges and the local cases gradually dominate the total cases,

with local cases accounting for 70.9% of the total cases (78 out of 110 cases). In stage (II), the daily number of COVID-19 confirmed cases increased rapidly and reached the peak of 44 new cases on March 19. After that, the daily number of cases gradually declined till April 4, 2020, when it dropped to below 5. A total of 753 confirmed cases were reported in stage (II), most of them were imported, accounting for 63.2% of the total cases. In stage (III), only sporadic new cases emerged every day. A total of 343 cases were reported within about 3 months, of which the vast majority (83.7%) were imported. From July 1, 2020, the epidemics in Hong Kong entered its stage (IV), during which the number of daily cases increased rapidly again with a peak of 122 cases on July 7, 2020, and then declined gradually. The epidemic intensity of stage (IV) was 2.7-fold, i.e., 2,066 vs. 753 total number of cases, higher than that of stage (II). Different from the previous stages, local cases dominated the epidemic in stage (IV), accounting for 86.5% of the total cases (1,787 out of 2,066 cases), while only 13.5% of the cases were imported (**Table 1** and **Figure 1**).

In Hong Kong, the pooled rAP was estimated at 23.1% (95% CI: 10.8–39.7%) from January 23 to July 31, and the rAPs were estimated at 22.6% (95% CI: 11.1–38.9%) among local cases and 38.7% (95% CI: 9.0–72.0%) among imported cases. In stage (I), the rAPs fluctuated considerably, especially in local cases. After entering stage (II), the rAPs were low at the beginning, but increased gradually as the epidemic progressed. At this stage, the increasing trends of rAPs of local and imported cases were similar, but the one for local cases was generally lower than that for imported cases. In stage (III), asymptomatic individuals were mainly imported, while the local cases were negligible. The rAPs were relative volatile in stage (III), similar to those in stage (I). In stage (IV), the rAPs of local cases were relatively stable, maintaining around 22%, while the rAPs of imported cases fluctuated greatly, reaching higher than 60% in about half of the time period (**Table 1** and **Figure 1**).

DISCUSSION

We developed a simple likelihood-based framework to estimate the instantaneous asymptomatic proportion of infectious

FIGURE 1 | The daily number of total **(A)**, imported **(C)**, and local **(E)** COVID-19 confirmed cases in Hong Kong. The daily reported asymptomatic proportions (rAPs) among the total **(B)**, imported **(D)**, and local **(F)** cases. In panels **(B,D,F)**, the red circles represent the daily rAP, where the circle size represents the sample size, the pink vertical bar represents the 95% confidence interval (95% CI), and the purple curve represents the crude rAP.

diseases and used the publicly available COVID-19 surveillance data in Hong Kong as an example for demonstration.

As an international metropolis, Hong Kong has a high population mobility. Imported cases account for a significant proportion of reported cases, particularly during the first epidemic. We found that the pooled rAP estimation of imported cases (38.7%) appears higher than that of local cases (22.6%). Several potential factors led to this result. Firstly, imported cases are mainly from the United Kingdom and the United States (34), and the asymptomatic rate reflects the comprehensive level of the importing countries. Some representative studies have shown that the asymptomatic infection rate is around 40% (35, 36), which is consistent with our estimated rAP at 38.7% (95% CI: 9.0–72.0) among imported cases. Secondly, imported cases are mainly returned from overseas study or tourism. They are mostly young people, with a large proportion aged from 15 to 24 (11, 34). However, elder people appear more likely to develop severe symptoms, as shown in the epidemic on the Diamond Princess cruise ship (24, 37). Thirdly, asymptomatic infections rarely seek medical advice and thus are less likely ascertained. However, during the outbreak, the Hong Kong government quarantined all arrivals, which can lead to more stringent testing and quarantine for imported than local individuals. As such, asymptomatic individuals in imported cases can be more fully captured.

The time series of the COVID-19 epidemic in Hong Kong included in our study was divided into four stages, of which stages (**II**) and (**IV**) were two discontinuous epidemic periods.

The trend of rAPs, proportion of imported cases, and rAPs of imported cases changed greatly between the two epidemic periods. During an epidemic, the testing coverage and the level of contact tracing should be constantly increased, which results in a significant increase of the detection rate of asymptomatic infected individuals (38), that is, leads to a gradual increase in instantaneous asymptomatic rates of both imported cases and local cases. Most Hong Kong residents who studied or traveled abroad returned on or before the first epidemic period (34). With the development of the epidemic, public awareness may gradually increase. COVID-19 infected cases with symptoms will choose to travel less, hence less likely to import into Hong Kong. Meanwhile, the suspension of most airlines and shipping to Hong Kong with a strengthened quarantine rate and the spread of portable devices such as thermometers have also contributed to the less imported cases. These factors played important roles in reducing the proportion of imported cases and increasing the rAPs of imported cases.

There were sporadic daily cases in stages (**I**) and (**III**). At these two stages, a slight change in the number of asymptomatic infected individuals could cause a drastic fluctuation of the rAPs; consequently, the confidence intervals of estimation are relatively large.

The data-driven rAP depends highly on the precise ratio of asymptomatic infected individuals and symptomatic cases. We found that the reporting of asymptomatic individuals may have significantly influenced the scale of case data, as

symptomatic cases are less likely to be incorrectly identified (or under-ascertainment rate to be relatively low). Therefore, on one hand, the under-ascertainment in asymptomatic individuals can result in an underestimation of the rAPs. On the other hand, if we assume the asymptomatic proportion ranging from 27.8 to 30.8% among clinically diagnosable COVID-19 cases as estimated in previous studies (19, 21), an average under-ascertainment rate of asymptomatic individuals in Hong Kong ranging from 22.0 to 32.5% is calculated backwardly.

For another aspect, asymptomatic COVID-19 cases may have important contributions to secondary infections (39). They can unknowingly spread the virus and are more likely to produce asymptomatic offspring, bringing severe battles for epidemic prevention and control (40). In this study, we proposed an analytical approach to estimate the instantaneous asymptomatic proportion of infectious diseases and, as a case study, to reveal the temporal patterns of COVID-19 transmission and spectrum. We believe that our study can bring an insight into understanding the transmission of COVID-19. It should be pointed out that our study still has several limitations. Firstly, our estimates rely on total and timely reporting of asymptomatic infected individuals. Alternatively, an overdispersion setting in the likelihood distribution can be incorporated to resolve inaccurate deterministic scenarios. Secondly, as a data-driven analysis, our estimates rely on the consistency of the statistical framework and reported COVID-19 case data.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://www.chp.gov.hk/files/pdf/local_situation_covid19_en.pdf.

ETHICS STATEMENT

The ethical approval and individual consents were exempted as the aggregated data used in this study are from public domain.

AUTHOR CONTRIBUTIONS

All authors conceived and conducted the research, wrote the draft, critically revised the manuscript, and approved the submission.

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