A New Approach to Modelling Pre-symptomatic Incidence and Transmission Time of SARS-CoV-2 Variants

Sam Li-Sheng Chen
Taipei Medical University College of Oral Medicine
Grace Hsiao-Hsuan Jen
Taipei Medical University College of Oral Medicine
Chen-Yang Hsu
National Taiwan University Institute of Epidemiology and Preventive Medicine
Amy Ming-Fang Yen
Taipei Medical University College of Oral Medicine
Chao-Chih Lai
National Taiwan University Institute of Preventive Medicine: National Taiwan University Institute of Epidemiology and Preventive Medicine
Yen-Po Yeh
Changhua Public Health Bureau
Hsiu-Hsi Chen (chenlin@ntu.edu.tw)
Institute of Epidemiology and Preventive Medicine https://orcid.org/0000-0002-5799-6705

Research Article

Keywords: COVID-19, Pre-symptomatic, Multi-state model, Stochastic Process

Posted Date: May 3rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1561446/v1

Abstract

We applied a four-state stochastic process to decipher the natural infectious process of SARS-CoV-2 superimposed with the disease axis of pre-symptomatic, asymptomatic, and symptomatic states. So doing provides new insights into how pre-symptomatic transmission and the proportion of asymptomatic cases have been affected by SARS-CoV-2 variants, NPIs, and vaccination. We fitted the proposed model to empirical data on imported COVID-19 cases from D614G to Omicron between March 2020 and Jan 2022 in Taiwan. The pre-symptomatic incidence rate was the highest for Omicron followed by Alpha, Delta, and D614G. The median pre-symptomatic transmission time (MPTT) (in days) increased from 3.45 (first period) ~ 4.02(second period) of D614G until 3.94 ~ 4.65 of VOC Alpha before vaccination but dropped to 3.93 ~ 3.49 of Delta and 2 days (only first period) of Omicron after vaccination. The MPTT of the second re-surge was longer than the first surge for each variant before vaccination but this phenomenon disappeared for Delta after vaccination. The proportion of asymptomatic cases increased from 29% of D-614G period to 59.2% of Omicron. Modelling pre-symptomatic incidence and transmission time evolving with SARS-CoV-2 variants throws light on the underlying natural infectious properties of variants and also reveals how their properties are affected by vaccination and NPIs.

1. Introduction

While most of countries and regions have provided a variety of mitigation strategies for containing the epidemic of SARS-CoV-2 during Coronavirus disease (COVID-19) pandemic, they are faced with the evolution of a series of SARS-CoV-2 variants from the wild type, D614G, and various kinds of VOCs including Alpha, Beta, Gamma, Delta, and Omicron.

It is well acknowledged that infectious properties such as generation time, series interval, latency, and incubation period varied with SARS-CoV-2 variants according to several previous studies that have already modelled the dynamics of infectious process for estimating the parameters of these infectious properties (Ali et al. 2022, Park et al. 2021, Pung et al. 2021, Campbell et al. 2021).

While these epidemic modelling studies have provided valuable information on contact patterns, transmissibility, and infectious period that form the evidence-based scheduled quarantine and isolation it is very rare to map such an intrinsic infectious process with the disease axis characterize by pre-symptomatic, symptomatic, and asymptomatic statuses of COVID-19 patients that are particularly useful for designing practical mitigation strategies. To have a better understanding of such a link between the intrinsic infectious process and the phenotypes of disease statuses plays an important role in epidemic investigation and contact tracing of cluster infection and also provides precision testing with reverse transcription polymerase chain reaction (RT-PCR) in conjunction with the scheduled interval for quarantining and isolating in order to reduce the subsequent community-acquired outbreaks. For instance, it would be very interesting to model transmission time from pre-symptomatic to symptomatic phase as the longer the pre-symptomatic transmission time the longer the interval for quarantine and isolation of suspected cases is required. More importantly, as three disease statuses are affected by

types of SARS-CoV-2 variants, the policy of NPI, and the administration of vaccine their influences can be modelled by the reciprocal relationship on the incidence rate between pre-symptomatic (non-persistent asymptomatic cases) and persistent asymptomatic cases. Since COVID-19 pandemic is a global health issue making use of a series of chronological information on imported COVID-19 cases provides a clue to throw light on these postulates.

We are motivated by applying the proposed stochastic process to the empirical data on Taiwanese imported cases from various countries and regions worldwide in different periods in parallel with the evolution of SARS-CoV-2 variants, the change in NPI, and the administration of vaccination. Using imported cases gives a clue to the global profiles of SARS-CoV-2 infection and containment measures during COVID-19 pandemic. In addition, our Taiwanese dataset provides a natural opportunity to model natural infectious process and disease progression from pre-symptomatic phase to symptomatic phase, on which we are based to provide evidence-based precision test and scheduled quarantine and isolation.

2. Methods

2.1 The Stochastic Model for Infectious Process of the Imported COVID-19 Case

Let X(*t*) denote a random variable for the state at time *t* realized by four states defined within state space, Ω = {uninfected (state 1), pre-symptomatic phase (PSP) (state 2), symptomatic phase (SP) (state 3), and asymptomatic phase (ASP) (state 4)}. Given time t, PSP and ASP belong to symptom-free state but the distinction between PSP and ASP is that the former would progress to SP (non-persistent asymptomatic) whereas the latter would remain free of symptom after infection (persistent asymptomatic).
Figure 1shows the entire infectious process from exposure to infectives, through ASP or PSP until SP for the imported COVID-19 cases accompanied with time to exposure, the arrival time, and the duration of quarantine and isolation of those suspected infectives.

There are several assumptions made for the proposed four-state stochastic process that are supposed to be biologically plausible.

1. The proposed model is progressive from uninfected to SP.
2. ASP would not surface to SP and can only be detected through RT-PCR test.

Note that there is a fraction of patients infected with SARS-CoV-2 will not present any clinical symptoms. We therefore applied the idea of competing risk model to PSP and ASP for those infected. Infected subjects, when going through the pathway of PSP, would have a finite infectiousness time from PSP to SP.

Following the random process of X(t), Fig. 1 also sketches an illustration of natural course of infection for *n* passengers from time staying abroad until the end of quarantine and isolation. They consisted of *r* imported COVID-19 cases and (*n*-*r*) susceptible individuals. As shown in Fig. 1, suppose the *i*th enrolled

individual had been in close contact with three types of COVID-19 infectives (including symptomatic, pre-symptomatic, and possible asymptomatic cases) (Ferretti et al. 2020) while staying abroad since calendar time t_1 (departure time). Upon the arrival time (t_2), this individual may have four possible outcomes as defined within Ω from the date of exposure to the date of arrival governed by the infectious course of SARS-CoV-2 infection.

We are very interested in estimating three parameters deriving from the above-mentioned four-state stochastic process. These include the incidence rate of pre-symptomatic and asymptomatic CPOVID-19 and the hazard from pre-symptomatic to symptomatic phase. The parameter of the latter will be converted to the median pre-symptomatic transmission time (MPTT). The proportion of asymptomatic cases will be also computed by using these parameters.

2.2 Empirical Data

To model the infectious process in connection with the four-state disease model of COVID-19, we targeted the imported cases of COVID-19 among inbound passengers around the world flown into Taiwan between March 2020 and Jan 2022. We divided the study period into seven epochs to cover different periods of emerging SARS-CoV-2 variants including the D614G, Variant of Concern (VOC) Alpha, and Delta, and the recent VOC Omicron. The seven epochs were named according to the corresponding dominant SARS-CoV-2 variants as follows.

- D614G-1: March-June 2020
- D614G-2: July-September 2020
- Alpha-1: October-December 2020
- Alpha-2: January-May 2021
- Delta-1: June-August 2021
- Delta-2: September-November 2021
- Omicron-1: December 2021-January 2022

It should be noted that we excluded domestic cases because they may contain unknown origin of contact history that may preclude us from estimating the relevant parameters governing the natural history of COVID-19. For each confirmed case, we retrieved data from a repository summarizing the information on imported cases reported by the Central Epidemic Command Center (CECC) in Taiwan (TCDC, 2020). In addition to personal attributes including age and sex, the time stamped on the date of arrival and departure from foreign countries, date of arrival at Taiwan, date of the occurrence of clinical symptoms, and date of RT-PCR test performed were abstracted from the CECC press. It should be noted that as the majority of inbound passengers are Taiwan residents who had been abroad and flown back after business the period between the date of departure and the date of arrival can be exploited for estimating three parameters of interest as below. We can also assume the date of departure would stay in the uninfected state because they would be requested for negative RT-PCR test negative before departure. Therefore, although the exactly date of exposure is unknown it can be assumed the date of exposure

must lie between the date of departure and the date of arrival. This forms the basis for building up the likelihood functions as below for estimating pre-symptomatic incidence and the median time of pre-symptomatic transmission. Following the guideline of Taiwan CECC, for subject with suspected symptoms of COVID-19 including fever, cough, short of breath, fatigue, myalgia, diarrhea, and anomaly in smell and test, they would be tested for SARS-CoV-2 infection with RT-PCR twice within 24 hours. For inbound passengers without symptoms, it is mandatory for these subjects to be isolated for quarantine for 14 days. The quarantined subjects will be tested for SARS-CoV-2 upon the occurrence of suspected symptoms during their 14-day quarantine (Taiwan Centers for Disease Control 2021). Information on the origin of country/region for the inbound cases were also collected. Supported by the empirical data of timeline through COVID-19 symptom development, we estimated the rates of progression from pre-symptomatic phase to symptomatic phase. Data on the number of passengers arrived at Taiwan with the information on the departure countries were retrieved from the open data source of Ministry of Transportation and Communications, Taiwan and Ministry of the Interior National Immigration Agency, Taiwan.

2.3 Transition probabilities of state transition

Let I(t) and i(t) represent cumulative distribution function (CDF) and probability density function (pdf) of being infected and staying in the PSP, namely the transition from state 1 to state 2 at time *t*. The two corresponding functions for the progression from PSP to SP (transition from state 2 to state 3) are denoted by F(t) and f(t). Let A(t) and a(t) denote both CDF and pdf for the occurrence of asymptomatic COVID-19.

The transition probabilities from uninfected to pre-symptomatic, symptomatic, and asymptomatic, and of staying in uninfected in the time interval of $\left(t_1, t_2\right)$ are derived with the following stochastic integration formula.

$$P_{12}\left(t_1, t_2\right) = \int_{t_1}^{t_2} i\left(s - t_1\right) \times \left[1 - F\left(t_2 - s\right)\right] \times \left[1 - A\left(s - t_1\right)\right] ds$$

1

Equation (1) represents the transition probability from state 1 (uninfected) to state 2 (PSP) between t_1 and t_2. The first and second element inside the integral of Eq. (1) indicate the process for an infected individual who entered into the PSP at calendar time *s* since time t_1 (the date of departure) as shown in Fig. 1 but has not developed into SP yet until time t_2. The third element is not allowed to enter into the ASP once become pre-symptomatic cases according to our model specification.

$$P_{13}\left(t_1, t_2\right) = \int_{t_1}^{t_2} i\left(s - t_1\right) \times \left[1 - A\left(s - t_1\right)\right] \times F\left(t_2 - s\right) ds$$

2

Equation (2) is the transition probability for an individual who had been exposed at time t_1 and entered into PSP at time s (first element) and turn into symptomatic case at time t_2 (second element). The third element asserts that it would not be possible to go the pathway of being ASP from t_1 to t_2

$$P_{14}\left(t_1, t_2\right) = \int_{t_1}^{t_2} a\left(s - t_1\right) \times \left[1 - I\left(s - t_1\right)\right] ds$$

3

Equation (3) is the transition probability for an individual who become asymptomatic at time *s* (first element) and would not follow the pathway of progression from PSP to SP (second element).

The complementary probability for an individual staying uninfected state would be derived as follows.

$$P_{11}\left(t_1, t_2\right) = 1 - P_{12}\left(t_1, t_2\right) - P_{13}\left(t_1, t_2\right) - P_{14}\left(t_1, t_2\right)$$

4

The most important information here is related to the probability of progression from PSP to SP in the time interval between arrival (t_2) and the end of quarantine (t_3),

$$P_{23}\left(t_2, t_3\right) = \int_{t2}^{t_3} f(r)\, dr$$

5

, which is equivalent to $F\left(t_3 - t_2\right)$.

Equation (5) is to provide the transition probability for a pre-symptomatic individual who develops symptoms at instantaneous time *r* during the time interval between t_1 and t_2.

2.4 Statistical Distribution of i(t) and f(t)

There are various statistical distributions that can be used for depicting each pdf of *i(t)*, *f(t)*, and *a(t)* as indicated above. The simplest form follows the exponential distribution for each one of them parameterized by λ_1-λ_3, which represent pre-symptomatic incidence rate, the progression rate from PSP to SP, and asymptomatic incidence rate in the language of epidemiology. For pre-symptomatic and asymptomatic rate, it would be very reasonable to use two Poisson distributions, an alternative expression of exponential distribution in terms of counts during time interval, for capturing the two parameters of each exponential distribution, λ_1 and λ_3, given the assumption of rare disease among a large susceptible population.

For the progression rate from PSP to SP in relation to *f(t)*, various forms can be adapted. According to the distribution of viral load from PSP to SP from literature (Sethuraman et al. 2020), we reckon that the log-

logistic form seems more appropriate than others like the Weibull distribution form because it is more likely to have a non-monotonic hazard function to describe the progression from pre-symptomatic to symptomatic phase with time. With log-logistic form, it is possible to have a hazard function which increases with time when disease progresses and turns to decrease beyond a time point when a patient starts to recover (Collett 2003). The hazard function of log-logistic form is expressed as

$$h(t) = \frac{e^{\theta}\kappa t^{\kappa-1}}{1+e^{\theta}t^{\kappa}} \; 0 \leq \mathrm{t}, \; \kappa > 0 \; (6)$$

The cumulative risk of developing symptomatic phase from t_1 to t_2 can be written as follows,

$$F\left(t_1, t_2\right) = 1 - \left(1 + e^{\theta} \bullet \left(t_2 - t_1\right)^{\kappa}\right)^{-1}$$

7

Despite this postulate, we attempt a serious of survival functions, including exponential and Weibull distribution, to compare the resulting distribution of emerging symptomatic cases by time with that of log-logistic form. Recall that the hazard from pre-symptomatic to symptomatic phase will be converted to the median pre-symptomatic transmission time (MPTT).

2.5 Parameter estimation with Bayesian Markov Chain Monte Carlo method underpinning

We used the Bayesian Markov Chain Monte Carlo (MCMC) method to estimate the incidence of pre-symptomatic and asymptomatic COVID-19 and the transition from PSP to SP with time following various distributions, including exponential, Weibull, and log-logistic distribution. For each model, the initial 5000 burn-in samples were discarded. Every 20th sample of the following 100,000 iterations was retained and comprised the posterior distribution of parameters of interests. The posterior mean and 95% credible interval of equal tails were reported for all estimates.

3. Results

Table 1 shows the estimated results of various four-state stochastic models with three corresponding distributions of the infectiousness time from pre-symptomatic phase (PSP) to symptomatic phase (SP). The estimated incidence of pre-symptomatic and asymptomatic cases was 131 (95% CI: 124, 139) and 122 (95% CI: 115, 130) per 100,000, respectively. For the transition from PSP to SP, the scale parameter of the exponential model was estimated as 0.2217 (95% CI: 0.2034, 0.2412), yielding 3.13 das (95% CI: 2.87, 3.41) of median pre-symptomatic transmission time (MPTT) from PSP to SP (Fig. 2). For the log-logistic model, the logit scale and shape parameters were estimated as -2.8675 (-3.1713, -2.5656) and 2.3420 (95% CI: 2.1590, 2.5295), leading to 3.40 days (95% CI: 3.15, 3.66) of MPTT. The corresponding parameters for the Weibull form were 0.1405 (95% CI: 0.1152, 0.1692) and 1.2173 (95% CI: 1.1383, 1.2958), which gave 3.73 days (95% CI: 3.40, 4.06) of MPTT.

Table 1
Estimated results for time-varying transitions from pre-symptomatic to symptomatic COVID-19 of three distribution modelled by using the four-state stochastic process

Transition rate	Exponential model		Log logistic model		Weibull model	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
State 1◊State 2, λ_1	0.00131	0.00124, 0.00139	0.00133	0.00125, 0.00141	0.00131	0.00124, 0.00139
State 2◊State 3, $\lambda_2(t)$						
Scale parameter	0.2217	0.2034, 0.2412	-2.8675	-3.1713, -2.5656	0.1405	0.1152, 0.1692
Shape parameter	NA		2.3420	2.1590, 2.5295	1.2173	1.1383, 1.2958
State 1◊State 4, λ_3	0.00122	0.00115, 0.00130	0.00118	0.00110, 0.00125	0.00122	0.00115, 0.0013

Figure 2 shows the hazard function by time since exposure for these three models. The log-logistic form revealed an increasing hazard in the first four days since exposure in contrast to the constant hazard for the exponential form or the monotonic increasing hazard for the Weibull form.

The results of the DIC statistics show that log-logistic form for fitting the pre-symptomatic infectious time had the lowest DIC (33597.59), followed by the Weibull distribution (33911.49) and the exponential distribution (33940.65) (Table 2). The model allowing for the period effect led to a smaller DIC given each of distribution, of which log-logistic still had the smallest DIC (31379.62). When we further considered both effects of period and area, all the DICs were further reduced. Again, the log-logistic form still had the smallest DIC (29255.44).

Table 2
The DIC statistics for the four-state stochastic models with and without the covariates of period and area given three distributions of pre-symptomatic transmission time

Model	Types of Distribution		
	Exponential	Log logistic	Weibull
Four-state stochastic model	33940.05	33597.59	33911.49
Four-state stochastic model regressing on period	31907.22	31379.62	31847.16
Four-state stochastic model regressing on period and area with a shared area effect in the second D614G period	29747.89	29277.98	30048.61
Four-state stochastic model regressing on period and area	29718.81	29255.44	29706.91

Figure 3 shows the heat map of the posterior mean of pre-symptomatic and asymptomatic incidence (per 1000 person-year), the proportion of asymptomatic cases, and the MPTT with adjustment for the period effect, including the first D614G period, the second D614G period, the first VOC Alpha period, the second VOC Alpha period, the first VOC Delta period, the second VOC Delta period, and the VOC Omicron. It is very interesting to note that three surges of the incidence rate of being PSP (Fig. 3 (a)) fit in with the evolution of the SARS-CoV-2 variants, namely, the old type dominated by the emerging variant. It can be clearly seen that the transition from PSP to SP accelerated when the emerging variant pre-dominated whereas the corresponding transition slowed down with a longer MPTT before the next emerging type (Fig. 3 (b)). The MPTT of the first D614G (3.45 days) was shorter than that of the second (4.02 days). This was also noted for VOC Alpha and Delta, while Omicron had the shortest MPTT (2.03 days) compared with other SARS-CoV-2 variants. The VOC Omicron was still rampant in the first period and would be expected to have the same pattern with a longer dwelling time afterwards. It is very interesting to see the proportion of asymptomatic increased with periods (Fig. 3 (c)) before Omicron emerged. This could be influenced by the administration of vaccine that led to more asymptomatic cases (Fig. 3 (d)). However, it could be also attributed to the change of border control policy upon the request of negative test three days before embarking at airport. The obvious decline of the proportion of asymptomatic cases after November 2021 was corresponding to the effect of vaccine waning after two-dose jabs across the world.

4. Discussion

The four-state stochastic process is proposed here to map the natural infectious process of SARS-CoV-2 infection with the dynamic of the disease axis captured by pre-symptomatic incidence, the distribution of MPTT before the presence of symptoms, and the proportion of asymptomatic cases. It was further applied to the empirical data on imported COVID-19 cases for different SARS-CoV-2 variants in chronological order during COVID-19 pandemic.

Implications for modelling the dynamics of disease axis in terms of biological plausibility are several-fold. First, the magnitude of pre-symptomatic incidence may cover main information on the axis of infection that starts from exposure to infection and further becomes infectives for infecting other susceptible persons, which may reveal the latency of virus replication and partial information on the generation time between infector and infectee. Second, the duration of MPTIT may reflect partial information on generation time and partial information the incubation time before the presence symptoms although our estimated MPTT may not be directly compared with the estimated generation time and the incubation time from previous studies (Ali et al. 2022, Park et al. 2021, Pung and Mak 2021, Hart et al. 2022, Abbott et al. 2022) as the definition is still different. Third, the separation of pre-symptomatic cases from asymptomatic case is to avoid the confusion of conventional use in defining asymptomatic cases in static property that actually consist of pre-symptomatic cases and asymptomatic cases at certain time point of infection axis. It is very interesting to note that the reciprocal relationship between the incidence rate of pre-symptomatic cases and asymptomatic cases by periods gives the severity of each variant and the administration of vaccine for reducing severity. Fourth, the log-logistic form suggests an increasing hazard for symptomatic phase in the initial days after being infected but

decreasing after the peak time. From the viewpoint of biological plausibility, this is consistent with the evidence that viral shedding changed over time since exposure (Sethuraman et al. 2020). The results of short Delta and Omicron VOC compared with Alpha VOC are consistent with the lower generation time in Delta VOC (Hart et al. 2022) and Omicron (Abbott et al. 2022).

Quantifying incidence of pre-symptomatic cases and MPTT also provides new insight into the translation of the changes in these parameters into the effectiveness of containment measures given each variant. Evaluation of these parameters in chronological order is indicative of the effectiveness of containment measures including NPI, testing, and vaccination varying with period in parallel with the evolution of SARS-CoV-2 variants. Such an application of the proposed model for developing the surveillance in border control of imported cases has been demonstrated by using Taiwanese data on imported cases which covered a range of SARS-CoV-2 variants from Alpha to Omicron between March 2020 and January 2022. The estimated results show that the incidence of the pre-symptomatic cases was aligned with the epidemic curve globally, starting from the initial 109 per 100,000 passengers in the first D614G epoch, dropping to 40 per 100,000 in the second D614G epoch due to the restriction of NPI, resurging to 163 when Alpha VOC preponderated, and decreasing to 117 in the second Alpha epoch. Both findings revealed 63% and 28% effectiveness of NPIs for D614G and Alpha VOC, respectively, before vaccination. The incidence rates of pre-symptomatic phase when vaccine is available were similar between two epochs of the Delta period. However, it is contrary to the expectation of higher incidence of pre-symptomatic cases for Delta compared with Alpha because the former should have higher transmission than the latter in light of the estimated basic reproductive number (R_0) reported in the previous studies (Campbell et al. 2021, Liu et al. 2021). The decline in the absolute incidence rate of Delta compared with that of Alpha indicated the possible effectiveness of vaccine in reducing the frequencies of contact when vaccine reduces the susceptible population and increases immunized population and also reduces the chance of transmission probability. The incidence rate resurged dramatically in the recent Omicron period. This is partially due to the lifting of all NPIs after full vaccination and partially due to the waning of vaccine after full vaccination. More importantly, the incidence of asymptomatic cases increased consistently when time went by from first D614G epoch to Omicron epoch. This is mainly caused by the advent of vaccine that renders asymptomatic cases become more likely and is also possible due to different transmissibility and the severe property of SARS-CoV-2 variants. For example, Omicron had high transmissibility but most of infective are milder than Alpha and Delta.

The estimates of MPTT by SARS-CoV-2 variants revealed the speed of infection pertaining to pre-symptomatic transmission for different kinds of variants. It is very interesting to note that Omicron compared with other variants had higher growth rate of infection that is also commensurate with higher strength of infection in relation to pre-symptomatic transmission. In this sense, the proposed stochastic process may not only capture the feature of the strength-based reproductive number (R_0) model but also accommodate the speed-based growth rate model, which also provide important information on the growth rate of natural infection process as emphasized by Anderson et al (2020). More importantly, it should be also noted that the estimated MPTT from pre-symptomatic to symptomatic phase by variants

has significant implications for providing the optimal length (day) of quarantine and isolation. Based on this finding the length of quarantine can be reduced from Alpha, Delta and Omicron.

The major limitation of this study is pertaining to the generalizability of the proposed methodology. As Taiwan COVID-19 epidemic is well controlled the empirical data based on community-acquired outbreak data across SRAS-CoV-2 variants are hardly available. This accounts for why we exploited COVID-19 imported cases for estimating relevant parameters when using the proposed four-state stochastic model. However, whether the findings obtained from imported COVID-19 cases in the current study are similar to those based on community-acquired outbreak data is still uncertain and is worthy of being investigated in the future study. The other aspect of generalizability is relevant to whether Taiwan COVID-19 imported cases can be representative of each variant worldwide. Such an external validation can be made if the proposed four-state stochastic model can be applied to the imported COVID-19 cases of other countries.

In conclusion, modelling natural infectious process superimposed with the disease axis from symptom-free to symptomatic states in parallel with the evolution of SARS-CoV-2 variants in chronological order not only provides new insight into infectious properties of SRAS-CoV-2 variants but also reveals how their properties are affected by containment measures and the coverage of vaccination.

Declarations

Funding

This study was funded by Ministry of Science and Technology, Taiwan (MOST 108-2118-M-038 -002 -MY3; MOST 109-2327-B-002-009). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by GH Jen, CY Hsu and AM Yen. The first draft of the manuscript was written by SLS Chen. CC Lai, YP Yeh, and TH Chen interpreted results. All authors provided input on the revision of the manuscript. All authors read and approved the final manuscript.

References

1. Abbott S, Sherratt K, Gerstung M, Funk S (2022) Estimation of the test to test distribution as a proxy for generation interval distribution for the omicron variant in England. https://doi.org/10.1101/2022.01.08.22268920. medRxiv

2. Ali ST, Yeung A, Shan S et al (2022) Serial Intervals and Case Isolation Delays for Coronavirus Disease 2019: A Systematic Review and Meta-Analysis. Clin Infect Dis 74(4):685–694. https://doi.org/10.1093/cid/ciab491
3. Anderson R, Donnelly C, Hollingsworth TD et al (2020) Reproduction number (R) and growth rate (r) of the COVID-19 epidemic in the UK: methods of estimation, data sources, causes of heterogeneity, and use as a guide in policy formulation. Report for The Royal Society Science in Emergencies Tasking – COVID-19 (SET-C) for communication to the Scientific Advisory Group for Emergencies (SAGE)
4. Campbell F, Archer B, Laurenson-Schafer H et al (2021) Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. Euro Surveill 26(24):2100509. https://doi.org/10.2807/1560-7917.ES.2021.26.24.2100509
5. Collett D (2003) Modeling Survival Data in Medical Research. 2nd Edition, Chapman and Hall, London
6. Ferretti L, Wymant C, Kendall M et al (2020) Quantifying SARS -CoV-2 transmission suggests epidemic control with digital contact tracing. Science 368:eabb6936. http://doi.org/10.1126/science.abb6936
7. Hart WS, Miller E, Andrews NJ, Waight P, Maini PK, Funk S, Thompson RN (2022) Generation time of the alpha and delta SARS-CoV-2 variants: an epidemiological analysis. Lancet Infect Dis S 1473–3099(22):00001–9. https://doi.org/10.1016/S1473-3099(22)00001-9
8. Liu Y, Rocklöv J (2021) The reproductive number of the Delta variant of SARS-CoV-2 is far higher compared to the ancestral SARS-CoV-2 virus. J Travel Med. Oct 11;28(7):taab124. https://doi.org/10.1093/jtm/taab124
9. National Immigration Agency, Ministry of the Interior, Taiwan. https://www.immigration.gov.tw/5475/
10. Park SW, Bolker BM, Funk S (2021) Roles of generation-interval distributions in shaping relative epidemic strength, speed, and control of new SARS-CoV-2 variants. https://doi.org/10.1101/2021.05.03.21256545. medRxiv
11. Pung R, Mak TM, CMMID COVID-19 working group, Kucharski AJ, Lee VJ (2021) Serial intervals in SARS-CoV-2 B.1.617.2 variant cases. Lancet 398(10303):837–838. https://doi.org/10.1016/s0140-6736(21)01697-4
12. Sethuraman N, Jeremiah SS, Ryo A (2020) Interpreting Diagnostic Tests for SARS-CoV-2 JAMA. 323:2249–2251. https://doi.org/10.1001/jama.2020.8259
13. TCDC, Taiwan Centers for Disease Control. https://www.cdc.gov.tw/En
14. Ministry of Transportation and Communications, Taiwan. https://www.motc.gov.tw/en/index.jsp

Figures

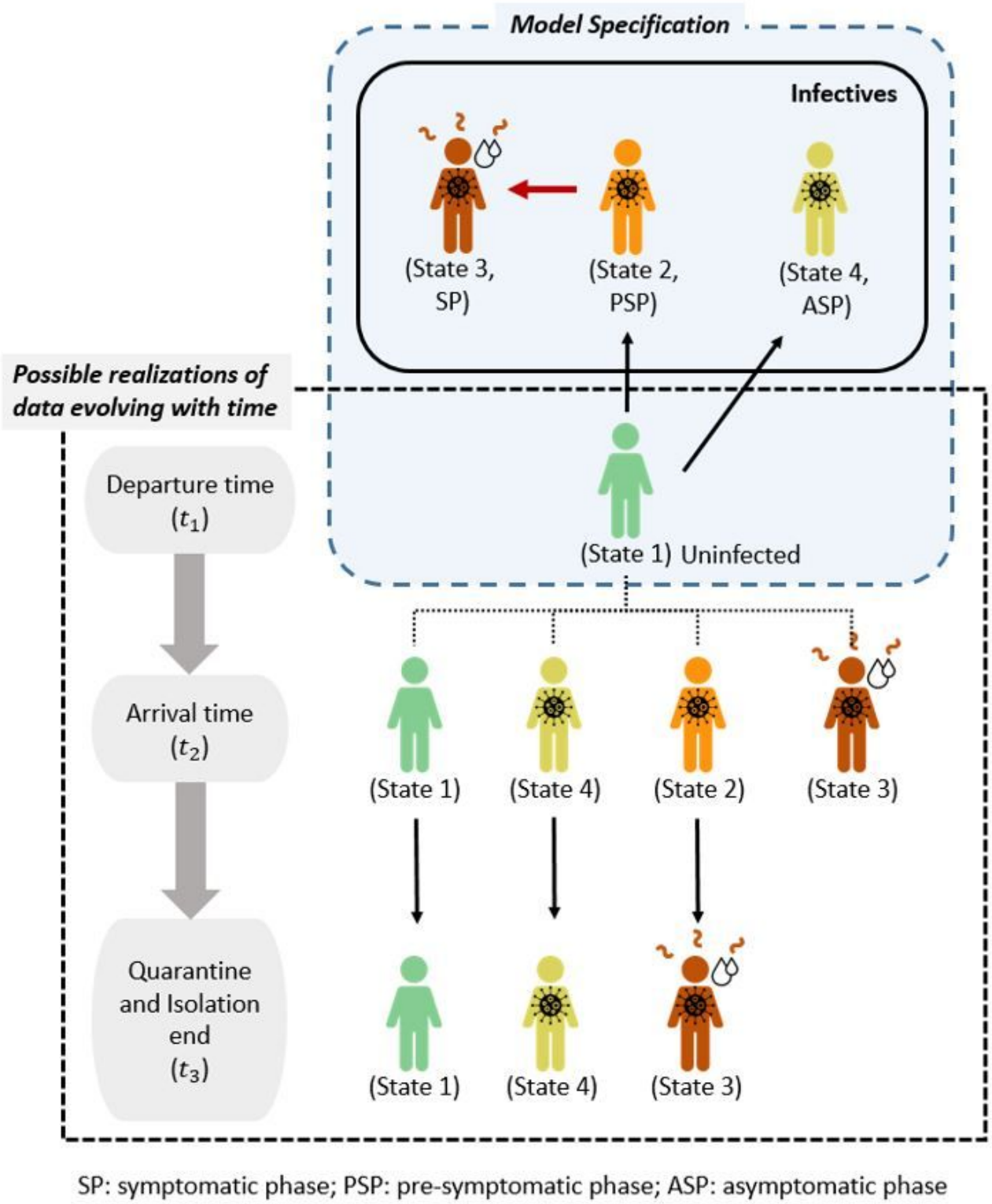

Figure 1

Model specification of pre-symptomatic and symptomatic COVID-19 and the realizations of data on states evolving with time

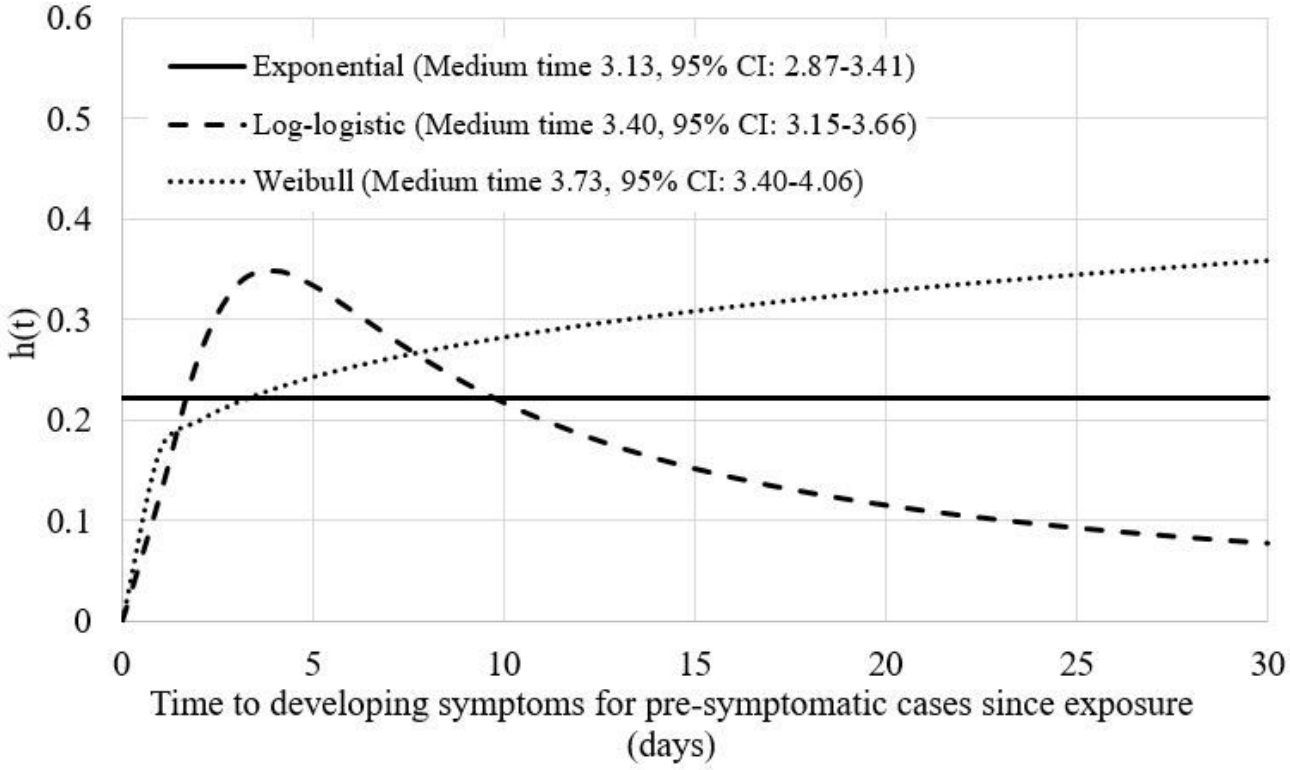

Figure 2

Time-varying hazard function with three distributions of pre-symptomatic transmission time

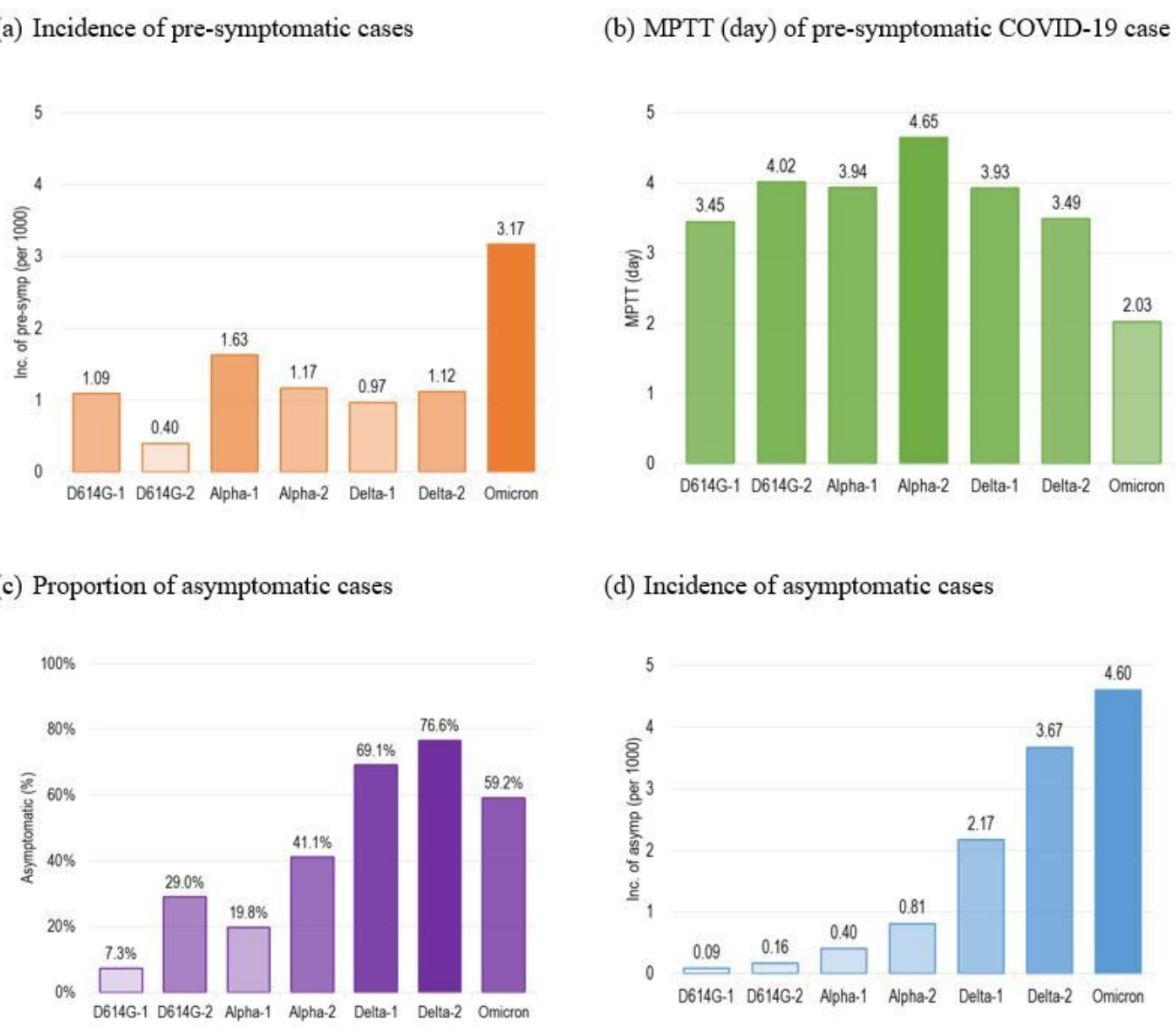

Figure 3

The posterior mean of incidence of pre-symptomatic cases, median pre-symptomatic transmission time (MPTT), and the proportion and incidence of asymptomatic case by period

D614G-1: March-June 2020；D614G-2: July-September 2020

Alpha-1: October-December 2020；Alpha-2: January-May 2021

Delta-1: June-August 2021；Delta-2: September-November 2021

Omicron: December 2021-January 2022