Relative Infectuousness of Asymptomatic and Symptomatic COVID-19 Infections - Analytical time table

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30 June 2021

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Abstract:

The question on the relative infectuousness of asymptomatic and symptomatic infections of COVID-19 is surrounded by contradictory clinical findings and confusion. This article undertakes a critical review of the available clinical literature on this topic, from the perspective of individual infection cycles and from the perpective of epidemiologic dynamics. Using the available results from the clinical and virological lietrature, we analyse how they fit in the time table of individual infection cycles, separately for the symptomatic and asymptomatic infection mode. The time table is based on a Susceptible-Infected-Resolve (SIR) mainframe, but the Infection compartment is sub-divided in 5 clinical stages for the symptomatic infection mode and 3 clinical stages for the asymptomatic infection mode. From the perpective of epidemiologic dynamics, the only period that matters is the time interval that infectives shed viable virus material, which is capable of self-replication in another host. The duration of this period can only be assessed by subjecting the positive RT-PCR tests samples to viral culture to isolate virus material that is able to self-replicate. Doing this on a daily basis reveals the time profile of effective infectuousness, separately for symptomatics and asymptomatics. For mild to moderate symptomatic cases we calculate that this period is 14 days on average, while for asymptomatic cases it is 9 days. Most of the replication-competent virus material is emitted during the first 4 days of this period, with few differences between symptomatics and asymptomatics. Because they shed virus over a longer interval, symptomatic infectives are likely to constitute the largest source of secondary infections. However, asymptomatic infectives have the largest average daily infectivity, because they shed most infective virus load during a short period. If the contact network of susceptibles has a sufficiently high share of asymptomatics in their early infection stage, the asymptomatic persons become the dominant source of secondary infections.

1. Introduction

Decision-making for public health policies is more complicated when infections, either bacterial or viral, are not immediately manifest from symptoms. The COVID-19 virus pandemic is characterised by two different infection modes, a symptomatic and an asymptomatic one. In the latter case, persons get infected without experiencing any symptoms, and during their unmitigated interaction they may disseminate the virus to other people. On top of that, the symptomatic infection mode has a pre-symptomatic stage during which the infected person, without knowing it, is already capable of transmitting the virus to others. Persons without symptoms tend to move freely in society and interact with non-infected people [8,70,79,35]. Symptomless infection transmission provides the virus with a distinct evolutionary advantage that allowed it to develop COVID-19 into a worldwide pandemic. The present paper proposes a new framework for analysing and quantifying the transmission probability of asymptomatic infections.

Most asymptomatic COVID-19 infections remain unidentified [4]. If identified, it is often in the context of outbreak-related contact tracing or localised community-wide testing (e.g. cruise ships). Only then are tested through RT-PCR swabs or serological antibody tests. Two large random-sampled, community-wide antibody test studies in Spain [57] and the United Kingdom [76] found that 32-33 percent of the persons who tested positive, reported to have had no symptoms. Reducing the number of undetected asymptomatic infections would requires mass testing of people without symptoms. This is only applied in a few regions and countries (e.g. China, Singapore). In the early stages of the current pandemic many countries had a lack of testing material, and national CDCs targeted all testing activity at symptomatic infectives and their contacts.

In the presence of symptomless infection modes, public health authorities require informed assessments of the relative infectuousness and dynamics of the unobserved, part of the pandemic. Attention for heterogeneous infection modes existed already for tuberculosis, which also has an unobserved infection mode. In the following citation from a recent paper on this topic [72], we might as well read COVID-19 where tuberculosis (TB) is mentioned:

> "*To advance toward TB elimination, this heterogeneity must be better understood and addressed. Drivers of heterogeneity in TB epidemiology act at the level of the infectious host, organism, susceptible host, environment, and distal determinants. These effects may be amplified by social mixing patterns, while the variable latent period between infection and disease may mask heterogeneity in transmission. Reliance on notified cases may lead to misidentification of the most affected groups, as case detection is often poorest where prevalence is highest*" [72] .

Since the second half of 2020, the increase in testing activity yielded a stream of scientific publications on the characteristics of asymptomatic infections [8,4,12,7, 53,70,26,81,52,25]. Nonetheless, at the moment of writing there is still a lack of consensus,

and even confusion regarding to the role of asymptomatics persons in the transmission of the COVID-19 virus, partly due to contradictory empirical findings. In *The BMJ* of December 2020, Pollock and Lancaster [58] concluded: "*The relations between viral load, viral shedding, infectiousness, and duration of infectuousness are not well understood*". Similarly, in April 2021, McEvoy et al. [46] concluded in *BMJ Open* that: "*Overall, there is currently only a limited number of published studies from which it is possible to derive a quantitative estimate of the relative infectiousness of asymptomatics. [..]. There is considerable heterogeneity in estimates of relative infectiousness highlighting the need for further investigation of this important parameter*". In May 2021, Chen et al. [16] state that "*data concerning the epidemiological features, viral shedding, and antibody dynamics between asymptomatic SARS-CoV-2 carriers and COVID-19 patients remain controversial*".

This paper delves into this matter by offering a new analytic framework on the concept of relative infectuousness of the two main infection modes. It is based on a stylised time table of individual infection cycles, and on recent research advances regarding the quantity of virus-shedding activity, and regarding the time pattern of the emitted virus quality. Using empirical inputs from a large number of clinical studies, our paper derives numerical estimates for the relative probability that susceptibles are infected by asymptomatic or symptomatic COVID-19 carriers.

The paper is structured as follows. The second section constructs an analytic time table for an infection model with parallel symptomatic and asymptomatic infection modes, each with linearly-related stages. The third section provides a stylised empirical version of this time table, building on clinical studies and meta analyses on the differences of infection modes, virus shedding, virus loads, and on the self-replication quality of the latter. This yields a stylised 'average' time path of individual infection cycles. The clinical sources are documented in two separate annexes. For symptomatics, we focus on the mild and moderate cases, because the severest cases are generally hospitalised and, from the perspective of epidemic dynamics, isolated. The fourth section proposes a rigorous quantitative definition of the relative infectuousness of the asymptomatic and symptomatic infection modes, further documented in a model annex. The fifth section discusses the implications of the results, and a final section concludes the paper.

2. Time table of symptomatic and asymptomatic infection cycles

The analytical set-up follows the Susceptible-Infected-Resolved model with with two parallel infection modes (symptomatic, asymptomatic) for the "Infected" compartment. Moreover, the "Infected" compartment is sub-divided in sequential sub-periods that differ by infection mode. The first column demarcates the jumps or switches between the main epidemic state variables (Susceptible, Infected, Resolved). The second column offers more detail by giving the switching points between different stages of the infection, demarcated by the events *p, v, m,* and *u*. Time is measured in

days. Table 1 presents the analytic stages between the infection event and the resolve of individual infection cases. The third column identifies the length of time intervals between the events. The two last two columns highlight the stages of the two main infection modes, i.e. the symptomatic (I) and the asymptomatic (A) mode.

Table 1   Transitions in individual infection cycles (symptomatic, asymptomatic)

State	Change event	Interval duration (in days)	Infection mode	
			symptomatic (I)	**asymptomatic (A)**
Susceptible (S)				
Infected	Infection (θ)		**stage 1** Incubation, non-infectuous for others	**stage 1** incubation period, non-infectuous for others
		θ - (p - 1)		
	Capable of infecting others (p)		**stage 2** Infectuous, but pre-symptomatic, shedding viable virus without knowing it	**stage 2** Infectuous, shedding viable virus, without knowing it, non-isolated $p - (u_a - 1)$
		p - (v-1)		
	First symptoms (v)		**stage 3** symptoms occur, shedding viable virus, but non-confirmed, no treatment, no isolation	
		v - (m - 1)		
	Test, treatment, isolation (m)		**stage 4** medical treatment and isolation, still shedding viable virus	
		m - (u_s - 1)		
	End of infectivity (u_a, u_s)		**stage 5** medical treatment and isolation, shedding non-viable virus $u_s - (r_s - 1)$	**stage 3** Non-infective, or shedding virus that is no longer viable $u_a - (r_a - 1)$
		u - (r- 1)		
Resolved (R) (removal from infected group)	Case resolves (r_a , r_s)			
			Cured / Immune (C) Dead (D)	Cured / Immune (C)

The symptomatic mode has five infection stages, and the asymptomatic mode three. Stage 1 in both COVID-19 variants is the incubation period in which the freshly infected cannot yet transmit the disease. Stage 2 in the symptomatic mode is the pre-symptomatic stage, in which an individual can unknowingly spread the infection. This

stage runs from event p (start transmission capability) to event v (onset of symptoms). The onset of symptoms starts stage 3 in which symptoms gradually become more serious and eventually medical assistance is sought for. After event m, stage 4 starts with confirmation of the disease, medical treatment and a form of isolation. Table 1 contains refines the infectivity concept, in line with Lavezzo et al.[35]. Event u_s is the moment at which the symptomatic still emits virus RNA and may still be ill, but is no longer emitting virus RNA that has the quality to self-replicate in another host. Event u_s is therefore the end of the effective transmission period from an epidemiological perspective. After that, stage 5 forms the end of the individual infection cycle in the symptomatic mode. The symptomatic continues to shed virus load until the resolve of the individual infection cycle (event r_s), which may be death in critical cases, or as the virus goes in remission, recovery and discharge of medical isolation.

The course of the individual infection cycle in the asymptomatic mode is much simpler. The presence of the asymptomatic infection mode can be assessed objectively by testing for emitting of virus RNA (RT-PCR test) or for the presence of antibodies (serological test). However, the asymptomatic person experiences and reports no symptoms during the full infection cycle. As an important consequence, most asymptomatics remain unidentified. The event p, at which the freshly infected person becomes capable of infecting others, passes unnoticed. And by definition, event v (onset of symptoms) also never happens in the asymptomatic infection mode. During stage 2, the asymptomatic person is capable of transmitting the disease to susceptibles and often mixes freely with susceptibles. Stage 2 ends when the infect person no longer sheds virus material that has the quality to self-replicate in another host (event u_a). Stage 3 is the final phase of the asymptomatic infection cycle. This stage has little implications, except that the person by chance could still be identified as COVID-19-positive in a PCR test, although the shedded virus material is not replication-competent any more. The resolve of the individual infection cycle (event r_a) follows in the same silent way, when the shedding of virus material does not even pass PCR test threshold values any more.

The time-window where unrestricted transmission of the infection to susceptibles may take place, has been shaded area in Table 1: stage 2 and 3 for the symptomatic mode, and stage 2 for the asymptomatic mode. These are the periods for which it is necessary to assess the relative infectuousness of both infection modes.

Note that Table 1 does not distinguish specific sub-intervals for time spent in home quarantaine, hospital treatment, or ICU treatment. While this can be important for medical capacity planning in the early outbreak phases, it is not essential for understanding the overall dynamics in the epidemic.

3. The individual infection cycles in an `average' quantitative version

This section sets out to construct an empirical version of Table 1, a stylised quantitative time table that measures the 'average' duration of all stages of the individual infection cycle in days. "Stylised" unescapably means that we lose statistical detail, for instance, with regard to case severity and national differences. "Average" means that we focus on the centre of the statistical distribution, using mean or median duration data. With regard to the symptomatic infections we focus on mild and moderately-severe cases. This assuages our relative disregard of the right-hand tail of the duration distribution. The stylised time-table of the individual infection cycles is based on the empirical evidence from a broad clinical and epidemiological literature. Annex I provides details on the distribution of the duration variable in the original source material (95% confidence intervals, inter-quartile range, standard deviation).

The gains of the simplifications occur in terms of the tractability and controllability of our results. The empirical model that we construct of both infection modes is consistent, offers an explanation for the confusion sketched in the introduction , and it is testable by future research.

Table 2 provides a flavour of the confusing empirical results regarding the duration of virus-shedding period for both infection modes. Virus shedding is in all cases measured through nasopharyngeal RT-PCR tests. The quoted clinical results in all cases report the mean or median number of days that virus loads on PCR swabs exceded a pre-selected threshold value. The results for symptomatic infectives do not show a consistent picture, given the relation between different clinicals intervals. The results for asymptomatic infectives may be upward biased, if sampling is based on contact tracing [37] instead of community-wide, aselective testing. Note that Table 2 does not provide strong evidence that the duration of virus shedding by symptomatics is longer than for asymptomatics.

The number of days with with above-threshold virus shedding is not enough to construct the time table of both infection modes. Two more aspects of virus shedding should be considered for evaluating infectuousness: the absolute magnitude of the virus load, and the replicative quality of the virus. The evidence strongly suggests that higher virus loads are positively correlated with the number of secondary infections and with the severity of the COVID-19 infection[81,1,78,36,62,77,29]. The second aspect is the replicative quality aspect of the virus RNA. Virus shedding is only relevant for infectivity, if the virus is able to self-replicate in new hosts. To derive the full empirical time table of the symptomatic and asymptomatic infection cycles, we build on many empirical findings. When obliged to select from heterogeneous findings, we prefer recent meta-analyses and reviews that use strict definitions, and control for observation period, sample size, non-selectivity in testing, and for endogenous

Table 2   Duration of virus-shedding, as measured from nasal PCR swabs

Clinical stage intervals [‡])	Mean length (days)	Median length (days)	Range min (C.I. 95%)	Range max (C.I. 95%)	Stand. deviation	Estimation details and sources
Symptomatics						
v to $(r_s - 1)$ \$)	21.8	..	..	..	7.6	S. Korea, [37]
m to $(r_s - 1)$ &)	25.2	..	..	..	4.9	S. Korea, [52]
m to $(r_s - 1)$ &)	..	18.0	15.0 [a])	22.0 [a])	..	S. Korea, n=328, [73]
p to $(r_s - 1)$ @)	17.0	..	15.5	18.6	..	meta study [12]
Asymptomatics						
m to $(u_a - 1)$ %)	..	9.5	7.0 [a])	14.0 [a])	..	S. Korea, *m* to first negative PCR test, n=68, [73]
m to $(r_a - 1)$ %)	..	14.5	11.0 [a])	21.0 [a])	..	S. Korea, *m* to full negative conversion, n=68, [73]
p to $(r_a - 1)$ §)		12.8				US CDC, [10], this section
p to $(r_a - 1)$ §)	19.1	..	..	..	7.5	S. Korea, [37]
p to $(r_a - 1)$ §)	22.6	..	..	..	4.0	S. Korea, [52]
Notes: [‡]) Codes refer to the Table 1; \$) onset symptoms to resolve; &) treatment / quarantaine / hospitalisation; @) time from transmission capability to resolve, for symptomatics; §) idem, for asymptomatics; %) time between first positive test and negative conversion; [a]) inter-quartile range.						

measurement impact from testing itself [8,4,12,7,53,70,26]. Moreover, for a consistent interpretation we build on a formal model that is separately presented in Annex I. Here we describe the procedure stepwise by evaluating the relevant empirical findings.

Virus shedding by symptomatics. A high nasopharyngeal viral load in RT-PCR tests increases the probability of secondary infections [29]. For symptomatics, the viral loads in the upper respiratory tract build up around the moment (*p*), peeking a few days before the first symptoms occur (event *v*). The viral load is highest in the first week of illness and then declines gradually. The mean duration of virus shedding is 17-18 days, according to a large meta study and a large clinical study [12,73] that are both cited in Table 2.

Shedding active virus by symptomatics. After subjecting positive PCR samples to viral culture, light and moderately severe infections, most studies [5,67] report no live and replication-competent virus beyond day *v+9*. The viral load remaining in PCR tests after *v+9* is apparently neutralised by the immune system and can no longer make copies of itself. Seroconversion occurs in 50% of patients at *v+7*, and by day *v+14* it is found in

all symptomatic patients.[77,83,49] For severe illness cases, replication-competent virus was found even later.[53,54,77] Also immunocompromised patients may emit culture-positive virus material for a longer period.[55,75] A different detection method[65,38] based on subgenomic RNA, also found rare cases of persistent active virus beyond *v+10*. Severe cases are in most countries hospitalised and isolated, thus reducing their impact on overall infection dynamics. Walsh et al. draw the following qualified conclusion: "*COVID-19 patients with mild-to-moderate illness are highly unlikely to be infectuous beyond 10 days of symptoms*".[75] For modelling the epidemiologic dynamics of secondary infections it may thus be sufficient to concentrate on the pre-symptomatic period plus the first nine illness days after onset.

Time structure in shedded active virus material by symptomatics. The development of infectuousness over time may be quantified using the time profile for successfully recovered replication-competent viruses from positive RT-PCR nasopharyngeal specimens. A large US cohort study [54] reports a time profile of virus-recovery success rates from daily positive PCR samples. The study itself presents the profile relative to event *v* (onset of symptoms), but for comparability with asymptomatics, who by definition have no symptoms, we transpose the profile to a common event in both infection modes, namely event *p* (infective acquires capability to transmit the virus). Clinical evidence summarised in Annex Table A2 finds that there are on average 4 days between events *p* and *v*. So the time profile of successfull virus recovery from daily positive PCR samples becomes: [54]

- interval *p* - (*p+3*)   : 71% of specimens with viable virus
- interval *(p+4)* -(*p+8*)   : 47% of specimens with viable virus
- interval *(p+9)* -(*p+13*)   : 30% of specimens with viable virus
- interval (*p+14*) - ($r_s - 1$) : 0% of specimens with viable virus

The first interval is the presymptomatic phase, which turns out to be the most infective sub-period.[24] Using the virus-recovery results of the third time interval as the reference point, the comparative infectuousness of the first interval is: $71/30 \approx 2.37$. Doing the same for all sub-periods, gives the daily infectuousness weights for the four sub-periods: 2.37—1.57—1—0. It means that, from the perspective of infection-transmission probability, one day from the first time interval counts the same as 2.37 days from the third interval. The days from the third interval can be labelled 'standard infection days'. The infectuousness of the full symptomatic infection cycle can thus be expressed in the number of 'standard infection days'. The first sub-period has four days, so its infectuousness weight is 9.48. The second and third sub-periods have five days, with infectuousness weights of, respectively, 7.85 and 5.0. Adding up, the average symptomatic accounts for 22.33 'standard infection days'. The average daily infectivity during the 14 days with shedding active virus material is 1.595 for symptomatics.

Virus shedding by asymptomatics. In March 2021, the US CDC[10] published the modelling assumptions for their latest epidemic planning scenarios for COVID-19.

Their preferred estimate is that viral-shedding by asymptomatics lasts 25 percent shorter than holds for symptomatic infectives. Using the estimate of 17-day shedding from a meta-study[12] (cf. Table 2), it implies that virus shedding for asymptomatics on average lasts 12.8 days. A small Chinese study [81] found that virus-shedding by nine asymptomatic infectives was 7-8 days. A South Korean study[73] of 68 asymptomatic infectives found that PCR test positivity disappeared in 50% of the cases after 9.5 days, but with a long tail in the distribution: still 10% positive PCR tests remained after four weeks, and 2.5% after five weeks. Given these results, the estimate of almost 13 days by the US CDC is a plausible average for the duration of virus shedding by asymptomatics. None of the eight studies[37,83,81,52,24,9,48,28] on which US CDC[10] bases its estimate, applied viral culture tests to assess the replication competence of shedded viral loads. The 13-day average for virus-shedding by asymptomatics must therefore be considered as an upper limit for the effective infectuous period.

Shedding active virus by asymptomatics. The viral loads shedded shortly after event *p* are comparable to those of symptomatics.[35,73] However, the decay of virus loads after the initial peak is faster than for symptomatic patients.[79,53,14,13,29,61,25,54,37,10, 12,84,73] A British study[67] on the kinetics of viable virus load found that time-related decay rates and the absolute levels of the virus load are the same for symptomatic and asymptomatic infectives. After 10 days, the probability of finding self-replicable virus material in serological testing dropped to 6%. A Korean study [73] of 68 asymptomatic cases found that 50% of them had their first negative PCR test after 9.5 days, 25% after 7 days, and 75% after 14 days. In all cases this most probably means that shedding of active virus material must have stopped a few days earlier, e.g. after, respectively, 5.5, 8 and 11 days. Also for asymptomatics there are long-shedding outlayers. Immuno-depressed, severely ill patients with other diseases than COVID-19 and infected by the asymptomatic COVID-19 infection mode, display shedding of active virus for a long time, even up to 70 days.[2] Due to their non-COVID-19 illness, such cases tend to occur in isolated and well-controlled environments, with little impact on overall epidemic dynamics.

Time structure in shedded active virus material by symptomatics. Given the evidence, it is plausible to assume that the asymptomatics' time pattern for shedding viable virus is comparable to that of symptomatic infectives, but for a shorter total duration (9 days, including the infection day) and with a steeper time-related decay. Compared to the time pattern for symptomatic infectives, the three sub-periods with culture-positive virus shedding are reduced with, respectively, 1, 2 and 2 days for asymptomatics:

- interval: $(p) - (p+2)$: 71% of specimens $(c.i. = 2.37)$
- interval: $(p+3) - (p+5)$: 47% of specimens $(c.i. = 1.57)$
- interval: $(p+6) - (p+8)$: 30% of specimens $(c.i. = 1.0)$
- interval: $(p+9) - (r_a)$: 0% of specimens $(c.i. = 0)$

The abbreviation *c.i.* stands for the comparative infectuousness weights of each sub-period, using the infectivity of the third period as reference, similar to the procedure for symptomatics. Using these *c.i.* values as weights we may aggregate the full personal infectivity cycle of asymptomatics in terms of these 'standard infection days'.

For the average asymptomatic this yields 14.82 'standard infectivity days' during the course of his/her infection cycle. This is only two-thirds of the corresponding figure for the symptomatics. However, the average daily infectivity for asymptomatics during their 9 days with shedding active virus material is 1.65, which is higher than for symptomatics due to the time profile of shedded replicable virus loads. Their less infective sub-periods are relatively shorter.

Quantifying clinical intervals of both COVID-19 infection modes. The key missing link for an empirical version of Table 1 were the events u_s and u_a, i.e. the moments at which the effective individual capability to transmit the disease ends for both COVID-19 infection modes. With the evidence provided in this section and in the detailed references of Annex 2, it is now possible to quantify the average duration of the effective individual infection cycles. Table 3 summarises the stylised empirical results per clinical interval of the COVID19 infection cycle.

Table 3   Clinical intervals COVID-19 infection cycle: stylised, empirics-based model values

Clinical stage intervals (legends in Table 1)	Average duration, in days	Details and references:
Symptomatic infectives		
stage 1: Incubation (latency), θ to p	2	Annex tables A1 and A2
stage 2: Presymptomatic infectivity, p to $(v-1)$	4	Annex table A2
stage 3: Onset symptoms to medical treatment, v to $(m-1)$	3	Annex table A4
stage 4: Shedding of active virus load: m to $(u_s - 1)$	7	[21], this section
Stage 5: Non-active virus-shedding to resolve : u_s to $(r_s -1)$	1-11	[21], Annex table A5
PM: stage 4+5, Treatment/hospital/ isolation: m to $(r_s -1)$	*8-18*	Annex table A5
Asymptomatic infectives		
Stage 1: Incubation (latency): θ to p	2	same as symptomatics
Stage 2: Shedding of active, virus load: p to $(u_a - 1)$	9	this section
Stage 3: u_a to $(r_a - 1)$	PM	undefined

Quantifying `average' duration is not equally different for all stages of the infection process. The virological research results with regard to the duration of stage 4 (shedding of viable virus material by symptomatic infectives) forms the least problematic source material. The available research results appear to converge on this issue, which allows to pinpoint event u_s quite precisely. Conversely, it is complicated

to determine the average duration of the medical care trajectory (period from event m to event r_s), because of the large national differences in the organisation and density of medical systems. The priority concern is that the length of stage 4 is in accordance with the international clinical research results. The length of stage 5 will be allowed to differ by country.

The effective infection cycle for symptomatics (stages 2-3-4) ends at event u_s and it lasts on average 14 days for mild and moderate cases. In the first half of this interval (7 days), the infected individual is non-tested, non-isolated and non-treated. This is followed by a period of again 7 days, during which the person is confirmed, treated and has some form of isolation. The effective infection cycle for asymptomatics (stage 2) lasts on average 9 days. Most often, this full period is without testing, isolation or treatment. An important result is also that the average daily infectuousness of asymptomatics is rather higher than lower, compared to symptomatics. The result corroborates some empirical findings.[25,83]

## 4. Relative infectuousness and epidemiological consequences

We searched the literature for a clear-cut, operational definition of the relative infectuousness concept, but we did not find a generally accepted methodology.[dx, ea, eb] Most of the literature agrees that virus-shedding activity matters, and that also the quality of the virus matters, but that is where the agreement stops. Here we define relative infectuousness as the product of (i) the mean number of virus-shedding days per infective, (ii) daily recovery rate of active, replicable virus material, and if applicable, (iii) downward mitigation of contacts with susceptibles through medical isolation or self-isolation.

The third element is added for symptomatics in particular. After confirmation, the latter enter stage 4 of their individual infection cycle (Table 3). It is plausible to assume that the frequency and intensity of their individual contacts with susceptibles will be reduced in this stage. While studies are available that quantify the generic contact-reducing effects of public-health policies, we did not find any study that quantifies the individual contact-reducing effects of being confirmed as a COVID-19 infective. We will therefore impose plausible factors to lower the comparative infectuousness weights (*c.i.*) from the day of seeking medical assistance (event m) up to the day that shedding of replicable virus material stops (event u_s). The reduction factors are: -50% at day m (day *p+7* in Table 3) and -66% per day during the rest of their effective infection period (days *p+8* to *p+13* in Table 3). The consequence of this medically-induced individual isolation is that the number of 'standard infection days' in the average symptomatic's personal infection cycle is reduced to 17.14 (down from 22.33, as was calculated in the preceding section). The next effect is that also the average daily infectivity over the total individual infection cycle drops to 1.22 (was 1.60). Calculation details can be found in Annex 1.

For asymptomatics, calculating the effects self-isolation or medically-induced isolation has much less relevance. If asymptomatic infections are identified through contact-tracing or community-wide PCR testing, it is likely that some form of isolation is strongly advised or imposed. Best estimates[7,4,10,8,48,35,37,70,53] of the share of asymptomatics vary between 15% and 67% of total infections, while only tiny numbers of asymptomatic infections are indeed identified. The effect of isolation after detection on asymptomatic infections is therefore probably small and may disappear in statistical noise.

It is now possible to put all elements together and to depict the comparative kinetics of infectuousness for both modes over the course of the full individual infection cycle. The vertical axis measures the shedding intensity of viable virus material, i.e. the amount of viable virus per shedding day, normalised by the amount of viable virus per day during the last sub-period of the individual infection cycle (*c.i.*).

Figure 1 Time pattern of average infectuousness over the individual infection cycle (based on shedding intensity of viable virus material)
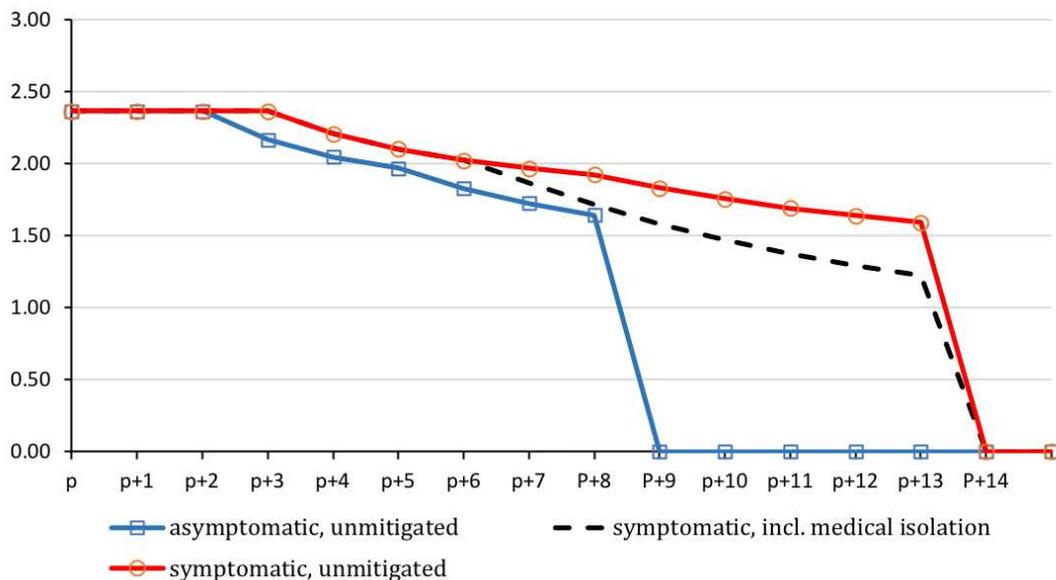
The dynamic pattern has implications for the infection risk. Suppose that there are 100 'average' susceptibles, who homogeneously interact with 50 'standard' asymptomatics and 50 'standard' symptomatics. All infectives are of the same infection cohort θ. Figure 1 shows that the susceptibles in the first three days have an equal probability of contracting the disease from an asymptomatic or symptomatic person. From day *p+3* onwards, the probability of contracting the disease from a symptomatic becomes dominant. However, once accounting for the impact of medically induced isolation, the dashed line in Figure 1 shows that the probability dominance of symptomatics shrinks rapidly after day *p+6*, and in *p+8* it has all but disappeared. Between day *p+9* and day *p+13*, the disease may only be contracted from a symptomatic person.

A quantitative measure for overall infectuousness per infection mode is the number of 'standard infection days' per individual infection cycle, as defined in section 3: for unmitigated symptomatics it is 22.33; for symptomatics with medically-induced isolation it is 17.14, and for asymptomatics it is 14.80. Hence, if all circumstances are the same, there is a higher probability of contracting the COVID-19 virus from a symptomatic. The main reason is that symptomatics shed active virus over a longer period. A second reason could be the phenomenon of super spreaders (severe symptomatic cases with large loads of viable virus and many contacts) who may generate a disproportionally larger infection risk. So far, we did not find any peer-reviewed empirical report that documents similar super spreaders among asymptomatics.[62,80]

The susceptible's actual probability of contracting COVID-19 from either infection mode depends not only on their relative infectuousness, but also on the composition of the susceptible's contacts network. Recall that the mean daily infectuousness of asymptomatics over the course of their (shorter) infection cycle is higher than for a symptomatic person. Figure 2 depicts how the probability of becoming infected by an asymptomatic becomes dominant if there are enough asymptomatic infectives in the susceptible's network. The shift occurs when 66% of the contacts group of the susceptible are asymptomatics. We corrected for the length of the infective cycle.

Figure 2 Composition of contacts network and probability of becoming infected by asymptomatic infectives

Share (%) of asymptomatic infectives in contacts network
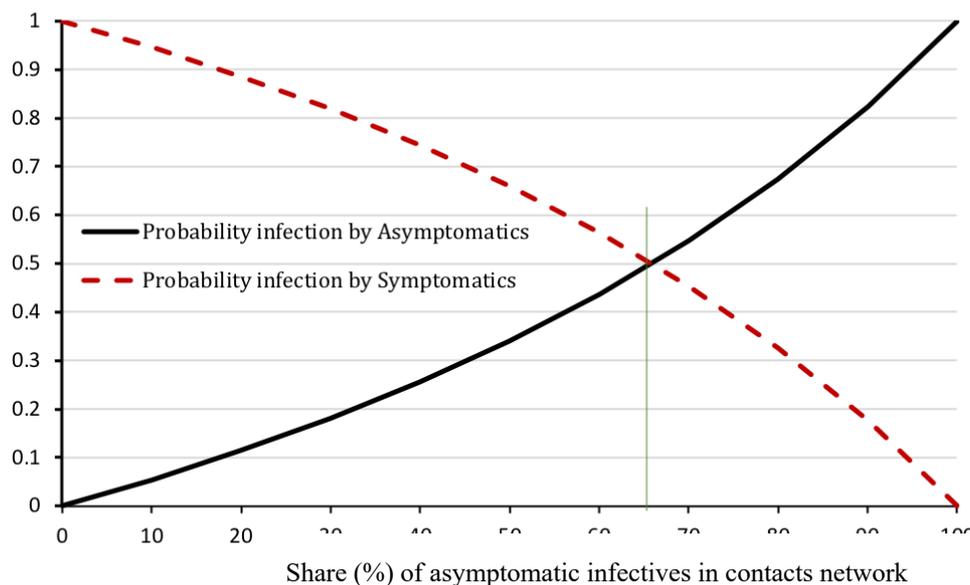
5. Discussion of the results

The analytical time table of the individual infection cycles could provide important inputs for public health policies and for epidemiologic research. The methodology

proposed in this paper can be adapted for use in case of other bacterial or viral infections that are characterised by partly symptomless transmission. It could answer several of the four key questions that were quoted from the recent literature in the introductory section:

- the relations between viral load, viral shedding, infectiousness, and duration of infectuousness are now framed in a consistent framework that may unify much empirical and clinical work;

- the paper provides a quantitative estimate of the relative infectiousness of asymptomatics.

- Many confusing and apparently contradictory finding on virus-shedding and infectuousness in earlier studies can now be interpreted. Early papers often described a cross-section of infected persons in different stages of their individual infection cycles. It is only logical that such mixing up results in contradictory findings. By controlling for the stage of the individual infection cycle, it becomes possible to interpret apparently contradictory and controversial findings and measurement in a single framework. We propose to treat infection data as infection-cohort panel data instead of cross-section data that only control for individual differences as age, sex and physical condition.

- When accounting for the change in medical knowledge since January 2020, changes in the testing activity, and contact-reducing public health policies, our results may also shed new light on certain anomalies in the data, for instance in strange patterns between current case fatality rates and the number of confirmed COVID-19 infections at the time that infection took place (event θ). If current case fatality rates correlate negatively with confirmed infections at time θ, this is most likely caused by asymptomatic infections. Such patterns are typically found at the start of a new infections wave. We address this issue in a separate companion paper.[31]

Our results, when found to be correct in further clinical research, should have consequences for the modelling of the epidemic. Most SIR/SEIR/SIRD models assume that the time during which individuals remain infectuous can be described by an exponential function and a single `exit rate' (γ) . This is biologically unrealistic, because it implies that the chance of recovery in a given time interval is independent of the time since infection. This leads to the distribution of infectuous periods being overly dispersed, whereas in fact they are often closely centred around the mean infection duration.[43] Non-exponential distributions make it necessary that the model keeps track of the time since infection. If the shedding of viable virus material indeed follows the time profiles that we have constructed from the empirical material, then it is clear that the bulk of the secondary transmissions must occur in the early part of the individual infection cycles.

6. Conclusions

The paper proposes an analytical time table of individual infection cycles for parallel symptomatic and asymptomatic infection modes. Symptomatic infectives with mild to moderate infections, can on average transmit the infection during 14 days. Most secondary transmissions occur in the first 7 days when the infectives are not isolated, do not yet have symptoms, and emit the largest daily loads of self-replicable virus material. After seeking medical assistance, the illness is confirmed, mostly followed by some form of isolation. This reduces the effective infectivity during the second half of the symptomatic infection cycle. The effective transmission period for asymptomatic infectives lasts on average 9 days, with also the largest infectuousness in the first half of this period. During their full infection cycle, the asymptomatics generally mix freely with susceptibles and are able to transmit the disease

We propose to calculate the relative infectuousness of both infection modes by the number of 'standard infection days'. Symptomatic infectives have the largest total number of 'standard infection days' and thus are likely to constitute the largest source of secondary infections. However, we also find that asymptomatic infectives have the largest average daily infectivity; they shed most infective virus load during a short period. This means that if the share of asymptomatics in the contact network of susceptibles is large enough (>66%), they may become the dominant source of secondary infections. Early detection of asymptomatic infectives by aselective community-wide testing is important and more research should be focused on their shedding of active virus material.

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Annex 1 Calculating relative infectuousness

The relative infectuousness of the symptomatic and the asymptomatic infection variant forms an important parameter for models that aim to explain epidemic dynamics. This holds for COVID-19 and for other infections that have partly unobservable transition phases. This annex describes our proposed indicator, using the infection stages as defined in Table 1. Let y be the number of days that an infected individual sheds virus material:

$$y_a = r_a - p \tag{A1}$$

$$y_s = r_s - p \tag{A2}$$

Virus shedding is only relevant for infection dynamics if the shedded virus material is capable of self-replicating in other hosts. Suppose we use positive nasopharyngeal RT-PCR test samples as input. For statistical significance of the results, take as many as possible daily RT-PCR samples of persons of whom the infection day (θ) can be tracked precisely. This can be done in track and trace settings to find secondary infectives linked to well-traced primary infectives.[e.g. 37, 35, 23] Subject the positive PCR samples subsequently to viral culture[e.g. 77,29,27] for recovering RNA material that is still capable of self-replicating in other hosts. Register the number of successful and non-successful cases in recovering active virus material, arranged by post-infection day. Create a statistical time profile for this variable, separately for each infection mode. Let u_s - 1 and u_a - 1 be the last day that, respectively, symptomatics and asymptomatics shed viable virus material. The positive amount of active virus material shedded on this last day ($\Omega_{s,u-1}$, $\Omega_{a,u-1}$) can be used as a numeraire to normalise the shedded amounts of active virus load (Ω) of all other days, and thus obtain a dimensionless indicator of relative infectuousness per shedding day:

$$\omega_{st} = \Omega_{st}/\Omega_{s,u_s-1} \quad with\ t \in p,..,(u_s - 1) \tag{A3}$$

$$\omega_{at} = \Omega_{at}/\Omega_{a,u_a-1} \quad with\ t \in p,..,(u_a - 1) \tag{A4}$$

To correct for measurement errors and volatility in daily measurements, it is advisable useful to apply `coarse-graining' by taking the mean score of multi-day sub-periods. Note that, by definition, the infectuousness weights are zero, once the shedded virus material is no longer capable of infecting others, so that $\omega_{st} = 0$ if $t \geq (u_s - 1)$ and $\omega_{at} = 0$ if $t \geq (u_a - 1)$.

The infectuousness weights ω_t can be used to obtain two important quantitative measures for individual infection cycles: aggregate infectuousness (Υ) and average daily infectuousness ($\bar{\varphi}$).

For most symptomatic individuals, the virus-shedding period splits into two parts, before and after medical confirmation (event m). Before m, the symptomatics mix relatively free with susceptibles thereby causing secondary infections. After m, most

symptomatics are likely to apply some form of self-isolation or are subjected to imposed medical isolation. This individual isolation effect lowers their daily infectuousness weights by a factor $0 \leq h_t \leq 1$. The aggregate infectuousness (Υ) indicator for symptomatics thus becomes a bit different from the one for asymptomatics:

$$\Upsilon_s = \sum_{t=\mathrm{p}}^{u_s-1} y_{st}^* \, \omega_{st}(1 - h_t) \tag{A5}$$

$$\Upsilon_a = \sum_{t=\mathrm{p}}^{u_a-1} y_{at}^* \, \omega_{at} \tag{A6}$$

in which y_{st}^* is the number of days that symptomatics shed active, viable virus material, and similarly y_{at}^* for asymptomatics.

The average daily infectuousness variable ($\bar{\varphi}$) over the individual infection cycle are:

$$\overline{\varphi_s} = \frac{1}{(u_s - 1) - \mathrm{p}} \, \Upsilon_s \tag{A7}$$

$$\overline{\varphi_a} = \frac{1}{(u_a - 1) - \mathrm{p}} \, \Upsilon_a \tag{A8}$$

Finally, the results allow to quantify the relative infectuousness (RI) of symptomatic and asymptomatic infection modes in a straightforward way:

$$RI_a = \frac{\Upsilon_a}{0.5(\Upsilon_a + \Upsilon_s)} \; ; \; RI_s = \frac{\Upsilon_s}{0.5(\Upsilon_a + \Upsilon_s)} \tag{A9}$$

The RI_a indicator has the following implications for the probability that a susceptible is infected by an asymptomatic rather than by a symptomatic. If a susceptible person with particular characteristics (age, sex, physical health condition) has 50 percent of symptomatics and 50 percent asymptomatics in her/his network, then RI_a predicts that the probability of getting infected by an asymptomatic is more than 50 percent. Otherwise, the RI_a indicator must be weighted with the local prevalence rates of asymptomatics and symptomatics. The other critical element is heterogeneity among susceptibles; e.g. susceptibles with particular characteristics are more likely than other susceptibles to be infected with an asymptomatic variant or a mild symptomatic variant.[e.g. 19,23,7]

Annex II   Empirical evidence on individual infection cycles

Table A1   Infection to onset of symptoms

Clinical stage intervals (legends in Table 1)	Mean length (days)	Median length (days)	Range min (C.I. 95%)	Range max (C.I. 95%)	Stand. deviat-ion	Estimation details and sources
θ to (v-1)		3.1 - 7.5				Singapore (SGP), [50]
θ to (v-1)		3 - 9	0	24		review paper [68]
θ to (v-1)		4	1	11		SGP, [59]
θ to (v-1)	4.2		3.5	5.1		Wuhan, CHN, n=24, [66]
θ to (v-1)	5.1					[24], [17], {34}, [22]
θ to (v-1)	5.2				3.7	CHN, Wuhan/ other, [33]
θ to (v-1)	5.2		4.1	7.0		CHN, Wuhan+, 10 cases, [40]
θ to (v-1)		5 - 6	1	14		CHN, [85], [50]
θ to (v-1)	5.3		4.5	5.99		meta-analysis, [39]
θ to (v-1)	5.8		5.0	6.7		Meta-study [45]
θ to (v-1)	5.99		4.97	7.14		SGP, [71]
θ to (v-1)	6	4 - 5	0	14		USA, CDC [10]
θ to (v-1)	6.7	6	3	9		CHN, SGP, Japan [44]
θ to (v-1)	6.4		5.6	7.7	1.7-3.7	CHN, Wuhan [3]
θ to (v-1)	6.6		0.7	19		Lombardy, Italy (ITA), n=5830 [11]
θ to (v-1)	7.2					serial interval, ITA, Vo', n=2850, [35]
θ to (v-1)	7.5		5.3	19		CHN, Wuhan, n=12 [40]
θ to (v-1)	8.68		7.72	9.7		CHN, Tianjin, [71]
Chosen interval parameter value	**6**					

Table A2   Duration pre-symptomatic infectivity

Clinical stage intervals (legends in Table 1)	Mean length (days)	Median length (days)	Range min (C.I. 95%)	Range max (C.I. 95%)	Stand. deviat-ion	Estimation details and sources
p to (v-1)	..	2	1	5	..	Ahui, CHN, [41]
p to (v-1)	4.0	..	..	..	..	Utah, USA, [38]
p to (v-1)	4.0	..	..	..	..	SGP, [71]
p to (v-1)	5.0	..	..	..	..	Tianjin ,CHN, [71]
Chosen interval parameter value	**4**					

Table A3   Duration of symptomatic non-isolated, non-tested infectivity

Clinical stage intervals (legends in Table 1)	Mean length (days)	Median length (days)	Range min (C.I. 95%)	Range max (C.I. 95%)	Stand. deviat-ion	Estimation details and sources
p to (m-1)	3.6	..	1	10	..	n=5830, ITA, Lombardy, [11]
p to (m-1)	4.6	..	4.1	5.1	..	CHN, Wuhan, n=207, [40]
p to (m-1)	5.8	..	4.3	7.5	..	CHN, Wuhan, n=45, [40]
p to (m-1)	..	6	5	7	..	cross-section of countries, [20]
p to (m-1)	7	..	6	8	..	Netherlands (NLD), CDC, [64]
Chosen interval parameter value	**6-7**					

Table A4   Duration interval from onset symptoms to testing & treatment

Clinical stage intervals (legends in Table 1)	Mean length (days)	Median length (days)	Range min (C.I. 95%)	Range max (C.I. 95%)	Stand. deviat-ion	Estimation details and sources
v to (m-1)	5.5	..	4.6	6.4	..	CHN, time to hospitalisation, meta-study, [39]
v to (m-1)	4	..	3	9	..	SGP, n=17, [59]
v to (m-1)	..	4.0	2.0 [a]	9.0 [a]	..	S. Korea, n=328, [73]
v to (m-1)	3.1	..	2.7	3.5	..	Faroe Islands, 186 cases [32]
v to (m-1)	3	..	1	14	..	Turkey (TUR), 360 cases, [25]
v to (m-1)	2.9	..	..	..	2.1	CHN [33]
v to (m-1)	..	2	0	4	..	USA, 1-3-'20 to 31-1-'21, [10]
Chosen interval parameter value	**3**					
Note: [a] interquartile range (25%, 75%).						

Table A5   Duration of medical treatment to case resolve

Clinical stage intervals (legends in Table 1)	Mean length (days)	Median length (days)	Range min (C.I. 95%)	Range max (C.I. 95%)	Stand. dev.	Estimation details and sources
m to $(r_s - 1)$		7	2	60		USA, n=111721, [21]
m to $(r_s - 1)$		8	2	60		USA, resolve: death, [21]
m to $(r_s - 1)$	11.2		8.0	17.3		CHN, resolve= death, [66]
m to $(r_s - 1)$	12.0	12.8	10	14		CHN, [22]
m to $(r_s - 1)$		14	6 [a]	26 [a]		Sweden, resolve= discharge [69]
m to $(r_s - 1)$		13 [b]	6 [a]	25 [a]		Sweden, resolve= death, [69] [b]
m to $(r_s - 1)$	17.8		16.9	19.2		resolve= death [74]
m to $(r_s - 1)$		18.0	15.0[a]	22.0 [a]		S. Korea, n=328, [73]
m to $(r_s - 1)$	18		13 [a]	25 [a]		CHN, resolve= hosp. discharge, [15]
m to $(r_s - 1)$	24.7		22.9	28.1		resolve= hospital discharge, [74]
Chosen interval parameter value	**8-18**					

Note: [a] interquartile range (25%, 75%). [b] Monthly patient cohorts display falling mortality.

Table A6   Duration from transmission capability to resolve

Clinical stage intervals (legends in Table 1)	Mean length (days)	Median length (days)	Range min (C.I. 95%)	Range max (C.I. 95%)	Stand. dev.	Estimation details and sources
Symptomatics						
p to $(r_s - 1)$	25					severe cases, [68]
p to $(r_s - 1)$	17.0		15.5	18.6		virus-shedding meta study [12]
Chosen interval parameter value	**17**					

Table A7   Duration from symptoms onset to resolve

Clinical stage intervals (legends in Table 1)	Mean length (days)	Median length	Range min (C.I. 95%)	Range max (C.I. 95%)	Stand. dev.	Estimation details and sources
v to $(r_s - 1)$	18.5		15.0	22.0		Wuhan, CHN, n=54, resolve= death, [82]
v to $(r_s - 1)$	22.0		18.0	25.0		Wuhan, CHN, n=137, resolve= discharge, [82]
v to $(r_s - 1)$	21.0		17.0	25.0		Wuhan, CHN, n=191 [82]
Chosen interval parameter value	**21**					

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