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Incubation period and serial interval of Covid-19 in a chain of infections in Bahia Blanca (Argentina)

Valentina Viego (https://orcid.org/0000-0001-5700-1133) [1]
Milva Geri (https://orcid.org/0000-0003-3265-3308) [1]
Juan Castiglia (https://orcid.org/0000-0002-3972-2946) [2]
Ezequiel Jouglard (https://orcid.org/0000-0002-5284-5422) [3]

Abstract *The objective of this work was to estimate the incubation period and the serial interval of Covid-19 from a sample of symptomatic patients in Bahia Blanca city during the period March-May 2020. We collected dates of illness onset for primary cases and secondary cases for the first 18 secondary patients infected with SARS-Cov-2. Estimations of incubation period are based on a log-normal distribution while we assume a Gamma distribution for the serial interval. In both cases maximum likelihood estimator was applied to estimate main parameters. Of the total of 18 cases of local transmission analyzed, 17% occurred in the presymptomatic and asymptomatic phase. The mean incubation period for symptomatic patients is 7.9 days (95%CI: 4.6, 11.1) considering the full sample and 7.5 days (95%CI: 4.1, 10.9) if the sample is restricted to the most certain cases. The median is 6.1 and 5.8 days respectively. The point estimation for the mean serial interval is 6.8 days (95%CI: 4.0-9.6). or 5.5 days (95%CI: 2.8, 8.1) for most certain pairs. The estimated median serial intervals were 5.2 and 4.1 days respectively. Comparisons with foreign estimates show that incubation period and serial interval could be longer in Bahia Blanca city than in other regions. Transmission from pre-symptomatic and asymptomatic is not negligible.*

Key words *Covid-19, Serial interval, Epidemiology, Bahia Blanca*

[1] Departamento de Economía, Universidad Nacional del Sur. Av. Leandro Niceforo Alem 1253, Bahía Blanca. Buenos Aires Argentina. vviego@criba.edu.ar
[2] Departamento de Epidemiologia, Secretaria de Saúde do Município da Bahía Blanca. Buenos Aires Argentina.
[3] Departamento de Ciencias de la Salud, Universidad Nacional del Sur. Buenos Aires Argentina.

Introduction

In Argentina the first case of the epidemic of Covid-19 was reported on March 3, 2020. As the WHO declared the disease as pandemic by March 11, 2020, health authorities decided to pose a mandatory lockdown since March 20, 2020 in order to prevent rapid propagation of infections and prepare the expansion of health infrastructure. After April 6, 2020, the government adopted a sequential easing of movements for selected economic activities combined with social distance measures, such as wearing masks and preserve the required distance between people.

Even though it is known that isolation and interventions that limit population movements and contacts curb the spread, health authorities still do not know how the virus is spreading within the national borders and in specific territories, like towns, cities or densely populated areas. Also, as testing is limited, the proportion of asymptomatic is not known, nor if contagion takes place during the pre-symptomatic phase of the disease. Besides the basic figures about confirmed cases, recovered or deaths, the development of local epidemiological indicators is still weak. In infectious diseases, one of the key indicators is the serial interval (SI from now on), defined as the time from illness onset in infector (index or primary case) to illness onset in infectee (secondary case). This indicator contributes to the understanding of the transmissibility of the disease[1]. Actually the SI is widely used to compute the effective reproductive number, that is the average number of secondary infections caused by each infector[2]. Estimates of the SI can only be obtained by linking the dates of illness onset between infector-infectee pairs. Thus, the main source of information emerges from clusters of infections.

Up to date, available figures of SI for Covid-19 come from a few regions, the majority belonging to regions with an early outbreak (Table 1). As was pointed out[3], more data about the serial interval is needed to evaluate interventions (contact tracing, selective quarantines, etc). If SI is overestimated quarantine interventions may be excessive. On the contrary, if SI is underestimated, interventions may be insufficient to curb the spread. At the same time, if SI is relatively short, symptomatic cases will emerge rapidly and health authorities will need to focus efforts in testing infrastructure and coordination. If SI takes longer it may be a signal of low asymptomatic transmission and less pressure on testing inputs.

Considering the incubation period, if transmission occurs mainly in the households the date of exposition is uncertain and restricts the estimations. Only 6 empirical studies provide figures about the time since exposition to illness onset (Table 2).

Materials and Methods

Between March 20, 2020 and May 8, 2020 36 cases were reported as positive for SARS-Cov-2 in Bahia Blanca city (Argentina). Local health authorities collected the date of illness onset and the date of exposure of each patient. As most of them emerged in clustered transmission it was possible to identify the infector-infectee pair in the chain.

From the total confirmed cases, 13 of them were imported and 23 were local cases. In addition, 4 of 23 local cases (17%) were asymptomatic up to May 8, 2020.

We have 17 observations of individual serial intervals emerged in 7 clusters of patients and 15 individual observations about the incubation period in patients who reported the date of exposition to their infector. Also, the date of exposition is probable in 3 cases, so we re-estimated the incubation period excluding those cases from the sample.

In most pairs (70%), the infection is part of hospital staff and contracted the disease in the workplace, in close contact with patients. For some of them (4 cases) the infector could not be clearly identified as more than one patient could have transmitted the virus. In those cases, we assigned the infector as the one exhibiting the closest period with the infectee´s illness onset. For that reason, we split the sample of pairs between certain and probable observations[10]. The subsample of certain pairs has 17 observations.

We assumed the serial interval follows a Gamma distribution and time to symptoms is distributed as a Lognormal[15]. The parameters were estimated using the *fitdist* command from *fitdistrplus* package in R using the maximum likelihood estimator, accepted as the best method to estimate the time to event from patient data[16,17]. Confidence intervals for the median were obtained using the quantile matching estimator.

We also estimate the mean SI from the sample of patients assuming uncertainty in probable dates of symptom onset. This requires a Bayesian approach, based on a numerical technique known as Markov Chain Monte Carlo (*mcmc*).

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Table 1. Serial interval estimations for Covid-19. International evidence.

Study	Region	Number of pairs	Median	Mean
(4)	Wuhan	6	not reported	7.5 [5.3-19.0]
(5)	S. Korea	12	4.0	6.6 [3.0-9.0]
(6)	China excl Hubei	468	not reported	3.96 [3.53-4.39]
(7)	China excl Hubei	35	not reported	5.1 [1.3-11.6]
(8)	China excl Hubei	71	4.0	4.27 (3.44)
(9) U	Hong Kong	21	not reported	4.4 [2.9-6.7]
(10)	Principalmente regiones Mainly Asian regions and cases reported in Germany	28*	4.0	4.7 [3.7-6.0]
(11) U	Lombardy (Italy)	90	not reported	6.6 [0.7-19]

Standard deviations in parenthesis; reported 95% CI in brackets; * The authors also provide estimations for 18 pairs with certainty about onset dates; U = unpublished, during peer review process.

Source: own based of references.

Table 2. Incubation period of Covid-19. International evidence.

Study	Region	N	Mean -days-	SD -days-
(12)	travelers from and to Wuhan (China)	88	6.4 [5.6-7.7]	2.3 [1.7-3.7]
(4)	China	10	5.2 [4.1-7.0]	no report
(13)	China excl Hubei	181	5.1 M [4.5-5.8]	no report
(14)	China excl Wuhan	52	5.0 [4.2-6.0]*	3 [2.1-4.5]
(7)	China excl Hubei	49	5.2 [1.8-12.4]	no report
(8)	China excl Hubei	65	5.33 5.0 M	3.3

M = median; * The mean is around 5.6 with SD of 2.8 when the inhabitants of Wuhan were included.

Source: own based on references.

This procedure estimates a posterior sample of SI distribution, which is a kind of average between prior beliefs of the distribution (e.g. Gamma) and observed data. The Bayesian approach can be more accurate in diseases with less known dynamics, like Covid-19.

Results

Figure 1 exhibits the chain of contagion (2 imported cases and 18 local transmission cases). The rest of 13 imported cases did not transmitted the virus locally. Until the cut-off date all infectors were recovered. For this reason, we assume no right censoring in the data.

In the sample of 17 infectee-infector pairs we found that 2 patients became infected during pre-symptomatic phase as their infector manifested symptoms after the exposition. Also, in the sample of cases with incubation dates, 1 case got infected from an asymptomatic infectious. Together, taking the proportion of transmission before symptom onset or from asymptomatic cases is 17%.

As the number of observations is modest and parametric estimation methods have asymptotic properties, we also checked the results with bootstrapping techniques (Chart 1).

Findings are presented in Table 3. The mean incubation period for symptomatic patients is 7.9 days (95%CI 4.6, 11.1) considering the sample of 15 cases patients and 7.5 days (95%CI 4.1, 10.9) if just the most certain cases (n = 12) are considered. The median is 6.1 (95%CI: 4.1, 9.2) and 5.8 (95%CI 3.6, 9.3) respectively.

In addition, 97.5% of symptomatic cases will develop symptoms before 13/14 days from exposition. Taking into account the results of the reduce sample of 12 cases, the upper limit of confidence interval increases to 17 days. These estimations are useful to decide the extent of quarantine in exposed individuals.

The point estimation for the mean serial interval is 6.8 days (95%CI: 4.0-9.6). Considering only the most certain pairs, the mean serial interval is estimated at 5.5 days (95%CI: 2.8, 8.1). The estimated median serial intervals were 5.2 (95%CI: 3.0, 8.1) and 4.1 (95%CI: 2.0, 6.9) respectively.

We found no substantive differences in the mean between the point estimations of parametric and Bayesian methods and also considering bootstrapping. Nevertheless, Bayesian methods show higher mean and median for the SI in the reduced sample than the ones estimated without uncertainty. This finding narrows the gap between the SI and the incubation period.

Figure 2 plots the histogram of observations and fitted distributions. Estimations show better adjustment of observed data for the SI than for the incubation period.

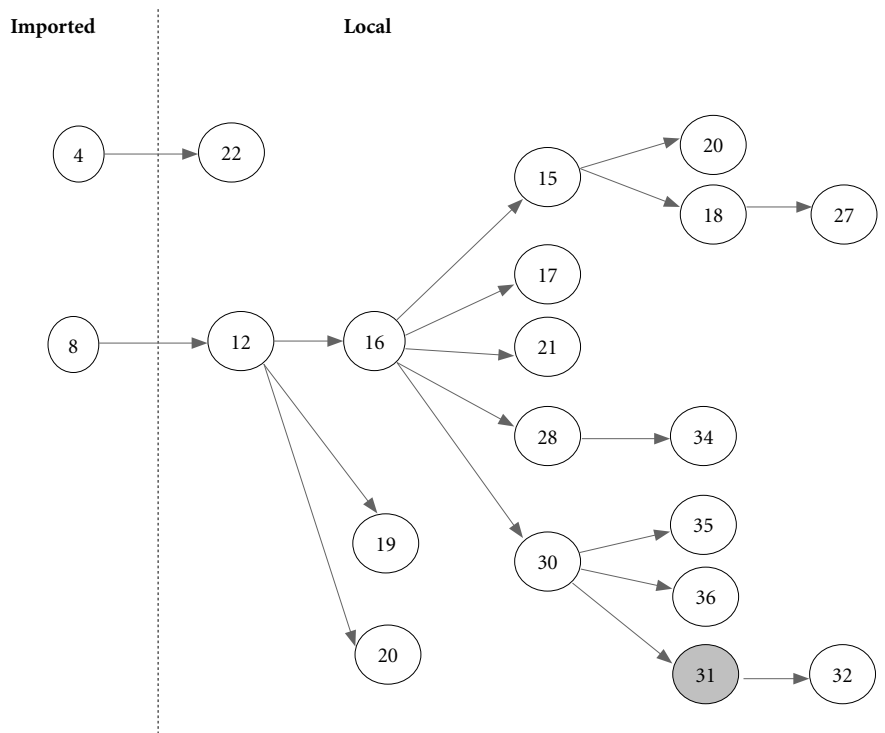

Figure 1. Covid-19. Chain of contagion in a sample of patients in Bahia Blanca city. March 20-May 8, 2020.

Source: own elaboration. The grey circle represents an asymptomatic case up to data cut-off.

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Chart 1. Estimations with parametric and non parametric bootstrapping (1000 repositions).

	Incubation period param bootstrapping	Incubation period param bootstrapping reduced sample	Incubation period non param bootstrapping	Incubation period non param bootstrapping reduced sample	Serial interval param bootstrapping	Serial interval param bootstrapping reduced sample	Serial interval non param bootstrapping	Serial interval non param bootstrapping reduced sample
Distribution	**Log normal**	**Log normal**	**Log normal**	**Log normal**	**Gamma**	**Gamma**	**Gamma**	**Gamma**
Mean (1)	6.08	7.30	6.21	7.36	6.6	5.24	6.68	5.46
Standard deviation (2)	5.76	5.63	6.06	5.86	5.47	4.36	5.61	4.63
CV (2)/(1)	0.95	0.77	0.98	0.80	0.83	0.83	0.84	0.85
n	15	12	15	12	17	13	17	13

Source: own calculations

Table 3. Incubation and serial interval in a sample of symptomatic infections.

	Incubation period	Incubation period for most certain cases	Serial interval Parametric approach	Serial interval for most certain pairs Parametric approach	Serial interval full sample Bayesian approach	Serial interval for most certain pairs Bayesian approach
Assumed distribution	**Log normal**	**Log normal**	**Gamma**	**Gamma**	**Gamma****	**Gamma****
Mean (1)	7.86 [4.63-11.09]	7.50 [4.11-10.89]	6.82 [4.04-9.61]	5.46 [2.84-8.08]	6.88 [2.0-32.14]	6.12 [1.31-31.73]
Standard deviation (2)	6.38 [3.42-15.87]	6.23 [3.21-16.99]	5.86 [1.80-3.69]	4.81 [2.48-13.12]	5.89 [2.09-17.76]	4.55 [1.47-16.77]
Median*	6.1 [4.06-9.18*]	5.76 [3.56-9.33*]	5.24 [2.96-8.11]*	4.13 [2.04-6.93*]	6.4 [4.6-9.2]	5.15 [2.95-7.50]
CV (2)/(1)	0.81	0.83	0.86	0.88	0.86	0.74
n	15	12	17	13	17	13
lnL	-43.31	-34.19	-49.21	-34.83	-52.52	-37.96

*CI for the median computed based on quantile matching estimator. Parameters differ only in the standard deviation estimation;
**It is the prior distribution, not the posterior. 95% CI and 95% CrI in brackets, depending on parametric or Bayesian estimation.
Source: Own calculations.

Discussion

The mean incubation period of Covid-19 estimated in Bahia Blanca city seems longer than the one reported in Asian regions. That implies a slower propagation as long as there is no substantial pre-symptomatic or asymptomatic transmission. Anyway a note of caution must be posed; as the coefficient of variation is also higher in Bahia Blanca, that heterogeneity in local spreading could be also higher than in other regions and/or the sample size is still low to get precise estimates. Yet[4], are based on a small sample of 10 cases and it reveals also lower variation than local case. That could favor the hypothesis of higher local dispersion relative to the international evidence.

On the other hand, own estimations show that some extreme cases may develop symptoms in 17 days. This implies that isolation measures for suspicious cases (close contacts of positive cases) of 2 weeks may be insufficient. Rather, 2.5 weeks could be a more precautionary isolation measure.

The estimations for the serial interval of Covid-19 suggest that symptom onset may take longer time to emerge between infectious, en-

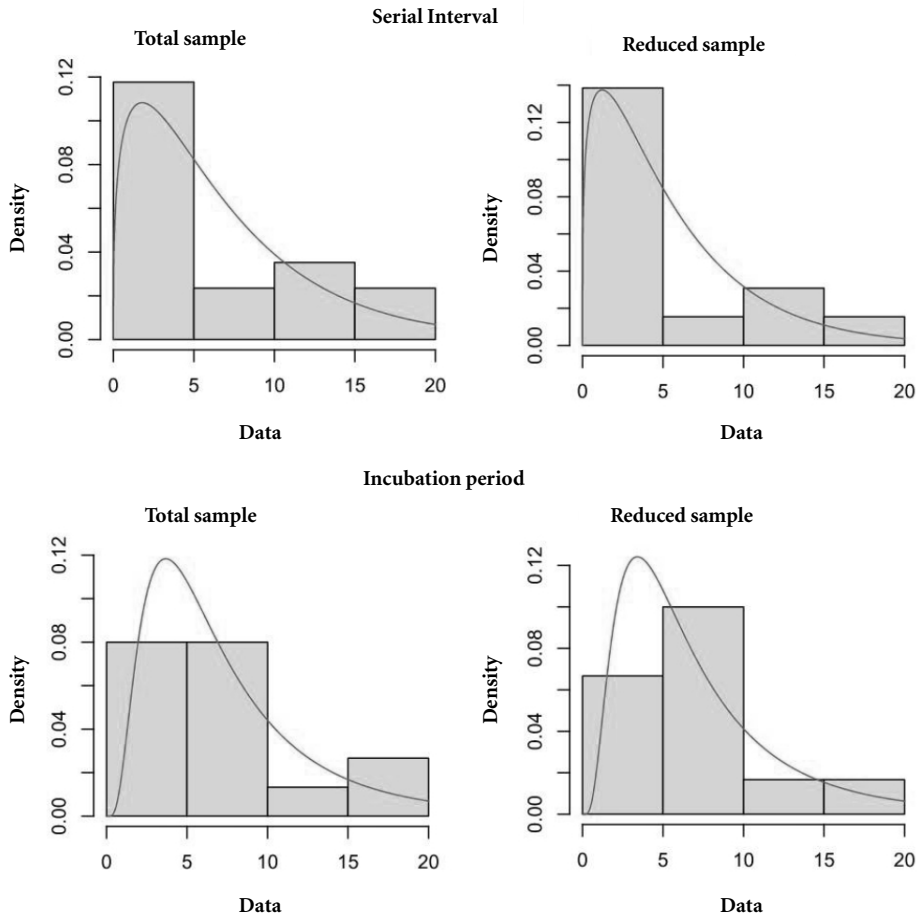

Figure 2. Empirical and theoretical density of serial interval and incubation period distributions for total and reduced sample. Results from parametric estimations.

Source: own elaboration.

larging the effective reproductive number (conditional to the rate of growth of cases). Nonetheless, local SI figures seem quite close to the ones reported for Lombardy (Italy).

The gap between the incubation period and the SI seems similar than the one estimated in foreign regions; presymptomatic transmission can occur between 1 or 2 days before symptom onset. That highlights the importance of contact tracing and timely isolation measures of patients' close contacts.

The present study has some limitations. First, from the first 36 cases 33% of symptomatic cases are hospital staff for whom contagion is clearly during the symptomatic phase and not before. If transmission takes place anywhere (beyond the household or closed places), pre-symptomatic contagion could be higher than estimated one.

Ethics Approval

Data collection and analysis of cases were conducted by the staff of the Epidemiology Department of the municipal government of Bahia Blanca. The Bioethics Council of the "Leonidas Lucero" hospital approved the research plan.

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Collaborations

Data collection was carried out by J Castiglia and E Jouglard. V Viego and M Geri made the estimates and the final report.

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