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Supplementary information

Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'

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Supplementary Information

Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'

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Text S1. Algorithm used to estimate the serial interval

Central overall estimate

For N (= 10,000) iterations we do the following steps

- For the subjects testing positive who report at least one contact and with missing onset date, impute the onset date from the onset-to-confirmation distribution (we sample with replacement from the observed onset-to-confirmation delays)
    - For each subject with observed or imputed onset date
        1. Randomly draw one of the contacts (we assume that each contact is equally probable; we assume that household members, on top of the named contacts, are contacts) to form an infector-infectee pair
        2. Calculate the absolute value of the difference between the onset dates of the infector-infectee pair. This is the serial interval of the infector-infectee pair
        3. Fit a gamma distribution to the serial interval distribution
            a) Output the mean, shape and scale parameters
- From the N realisations, calculate the mean of the serial interval mean, shape and scale parameters. These give the central serial interval estimates.

95% confidence interval of the overall estimate

For N (= 10,000) iterations we do the following steps

- We sample with replacement the subjects testing positive who report at least one contact
- For the sampled subjects testing positive and with missing onset date, impute the onset date from the onset-to-confirmation distribution (we sample with replacement from the observed onset-to-confirmation delays)
    - For each subject with observed or imputed onset date
        1. Randomly draw one of the contacts (we assume that each contact is equally probable; we assume that household members, on top of the named contacts, are contacts) to form an infector-infectee pair
        2. Calculate the absolute value of the difference between the onset dates of the infector-infectee pair. This is the serial interval of the infector-infectee pair
        3. Fit a gamma distribution to the serial interval distribution
            a) Output the mean, shape and scale parameters
- From the N realisations, calculate the 2.5 and 97.5 percentiles of the serial interval mean, shape and scale parameters. These give the 95% CI of the central serial interval estimates.

Central estimate for the pre-/post- lockdown period

For N (= 10,000) iterations we do the following steps

- For the subjects testing positive who report at least one contact and with missing onset date, impute the onset date from the onset-to-confirmation distribution (we sample with replacement from the observed onset-to-confirmation delays)
    - For each subject with observed or imputed onset date
        1. Randomly draw one of the contacts (we assume that each contact is equally probable; we assume that household members, on top of the named contacts, are contacts) to form an infector-infectee pair
        2. Calculate the absolute value of the difference between the onset dates of the infector-infectee pair.This is the serial interval of the infector-infectee pair
        3. Split the serial intervals into two groups:

a) Pre-lockdown: if the onset dates of both the infector and infectee are before 24 Feb 2020 (the start of the lockdown)
b) Post-lockdown: if the onset dates of both the infector and infectee are after 24 Feb 2020 (the start of the lockdown)
c) If the onset dates of the infector-infectee pair are either sides of 24 Feb 2020 (the start of lockdown), compute the time between onset of the infectee and start of the lockdown and between the lockdown and the onset of the infector; if the time between onset of the infectee and start of the lockdown is larger than the time between the lockdown and the onset of the infector, assign the pair to the post-lockdown period. Otherwise assign the pair to the pre-lockdown period.

4. Fit a gamma distribution to the serial interval distribution in the pre- and post-lockdown group
    a) Output the mean, shape and scale parameters

- From the N realisations, calculate the mean of the serial interval mean, shape and scale parameters of each group. These give the central serial interval estimates.

<u>95% confidence interval of the pre-/post- lockdown estimate</u>

For N (= 10,000) iterations we do the following steps

- We sample with replacement the subjects testing positive who report at least one contact
- For the sampled subjects testing positive and with missing onset date, impute the onset date from the onset-to-confirmation distribution (we sample with replacement from the observed onset-to-confirmation delays)
    - For each subject with observed or imputed onset date
        1. Randomly draw one of the contacts (we assume that each contact is equally probable; we assume that household members, on top of the named contacts, are contacts) to form an infector-infectee pair
        2. Calculate the absolute value of the difference between the onset dates of the infector-infectee pair. This is the serial interval of the infector-infectee pair
        3. Split the serial intervals into two groups:
            a) Pre-lockdown: if the onset dates of both the infector and infectee are before 24 Feb 2020 (the start of the lockdown)
            b) Post-lockdown: if the onset dates of both the infector and infectee are after 24 Feb 2020 (the start of the lockdown)
            c) If the onset dates of the infector-infectee pair are either sides of 24 Feb 2020 (the start of lockdown), compute the time between onset of the infectee and start of the lockdown and between the lockdown and the onset of the infector; if the time between onset of the infectee and start of the lockdown is larger than the time between the lockdown and the onset of the infector, assign the pair to the post-lockdown period. Otherwise assign the pair to the pre-lockdown period.
        4. Fit a gamma distribution to the serial interval distribution
            a) Output the mean, shape and scale parameters
- From the N realisations, calculate the 2.5 and 97.5 percentiles of the serial interval mean, shape and scale parameters. These give the 95% CI of the serial interval estimates.

Text S2. Algorithm used to estimate the reproduction number from transmission chains

Central estimate:

For N (= 10,000) iterations we do the following steps

- For all subjects testing positive with missing onset date impute the onset date from the onset-to-confirmation distribution (we sample with replacement from the observed onset-to-confirmation delays)
- For each subject with observed or imputed onset date
    - Identify the infector-infectee pairs using the contacts reported in the dataset (including family members)
        1. If the contacts of the subject have onset of symptoms before the subject, we assume that the contacts are infectors; otherwise we assume that the contacts are infectees.
        2. If an infectee has multiple potential infectors, randomly sample the infector.
    - If the subject reports no contacts, impute the infector as follows:
        1. Sample from the serial interval distribution before or after lockdown according to the onset of symptoms of the subject.
        2. Identify all potential infectors assuming an average infectious period of 4 days (i.e. those with date of onset in the interval [date of onset of the infector – 4 days, date of onset of the infector].)
            a) If there are no potential infectors go back to step 1 and resample an onset date for the infector.
        3. Randomly sample the infector from the potential infectors
- Divide all infectors into two groups, according to their onset date:
    - Pre-lockdown group: infectors with date of symptom onset before 20 Feb 2020
        - Calculate the mean number of infectees – this is a realisation of R
    - Post-lockdown group: infectors with date of symptom onset after 20 Feb 2020
        - Calculate the mean number of infecteees - this is a realisation of R
- The central estimates of the reproduction number before/after the lockdown are given by the mean of the R estimates from the N iterations, respectively calculated on the pre-/post- lockdown group.

95% confidence interval:

For N (= 10,000) iterations we do the following steps

- Sample with replacement the subjects testing positive
- For the sampled subjects with missing onset date impute the onset date from the onset to confirmation distribution (we sample with replacement from the observed onset to confirmation delays)
- For each subject with observed or imputed onset date
    - Identify the infector-infectee pairs using the contacts reported in the dataset (including family members)
        1. If the contacts of the subject have onset of symptoms before the subject we assume that the contacts are infectors; otherwise we assume that the contacts are infectees.
        2. If an infectee has multiple potential infectors, randomly sample the infector.
    - If the subject reports no contacts, impute the infector as follows:
        1. Sample from the serial interval distribution before or after lockdown according to the onset of symptoms of the subject.

2. Identify all potential infectors assuming an average infectious period of 4 days (i.e. those with date of onset in the interval [date of onset of the infector – 4 days, date of onset of the infector].
    a) If there are no potential infectors go back to step 1 and resample an onset date for the infector.
3. Randomly sample the infector from the potential infectors

- Divide all infectors into two groups, according to their onset date:
    - Pre-lockdown group: infectors with date of symptom onset before 24 Feb 2020
        - Calculate the mean number of infectees – this is a realisation of R
    - Post-lockdown group: infectors with date of symptom onset after 24 Feb 2020
        - Calculate the mean number of infecteees - this is a realisation of R
- From the N realisations, calculate the 2.5 and 97.5 percentiles of the R realisations. These give the 95% CI of the R estimates.

Text S3. Role of asymptomatic individuals in transmission

The presence of a significant number of asymptomatic SARS-CoV-2 infections raises questions about their ability to transmit the virus. To address this issue, we conducted an extensive contact tracing analysis of the 8 new infections identified in the second survey (**Supplementary Table S1**). Three of the new infections reported the presence of mild symptoms and did not require hospitalization. Subject 1 shared the same flat with symptomatic infected relatives. Subject 2 had contacts with four infected relatives who did not have any symptoms at the time of contact. Subject 3 reported contacts with two infected symptomatic individuals before the lockdown. Five of the eight new infections showed no symptoms; Subject 4 shared the same flat with symptomatic infected relatives. Subject 5 reported meeting an asymptomatic infected individual before the lockdown; Subjects 6 and 7 did not report any contact with positive individuals and Subject 8 shared the same flat with one asymptomatic and one symptomatic relative.
We also found evidence that transmission can occur before the onset of symptoms, as detailed hereafter for a family cluster. Subject A (**Supplementary Table S2**) was the first confirmed SARS-CoV-2 infection in the family, detected on February 22: the subject showed mild symptoms of the disease on February 22, was admitted to the Infectious Diseases unit on February 25 and subsequently discharged on February 29, with quarantine restrictions. The partner (Subject B) and children (Subjects C and D) tested positive on February 23 but showed only mild symptoms and did not require hospitalization. Subject A reported attending a family gathering three or four days before symptoms onset, together with a parent (Subject E) and three other siblings (Subjects F, G, and H). At that time, all of them were healthy. Nasal and throat swabs confirmed the presence of viral RNA in all family contacts. The transmission dynamics within this family clearly show that SARS-CoV-2 transmission occurred in the early stages of infection and in the absence of symptoms.

Table S1. Contact tracing of all new infections detected in the second survey

		with symptoms		without symptoms	
new cases at second survey (ID)		cohabitants	other contacts	cohabitants	other contacts
with symptoms	Subject 1 (zVOcHfvV)	2			
	Subject 2 (cbyQPPfZ)				4
	Subject 3 (JIIoYHyp)		2		
without symptoms	Subject 4 (EfZNPYyW)	1	1		
	Subject 5 (bopLYQcy)				1
	Subject 6 (heanXjZj)				
	Subject 7 (ZerTaDBI)				
	Subject 8(CDKdBamE)	1		1	

Table S2. Subjects in a family cluster, with the corresponding anonymous ID

Subject	ID
A	FxZZNlJK
B	uhaqSrJj
C	VLRIycjD
D	kBnjzTDk
E	hswRareX
F	Not included in the dataset (not resident in Vo')
G	ChOlOFXm
H	cbyQPPfZ

Table S3. Frequency of comorbidities in symptomatic and asymptomatic SARS-Cov-2 infected individuals*

	symptomatic		asymptomatic		
Comorbidity*^	present	absent	present	absent	p
Diabetes	1	24	3	13	0.28
Dyslipidemia	1	24	3	13	0.28
Hyperuricemia	1	24	1	15	1
Hypertension	14	11	6	10	0.34
Cardiological disease	2	23	2	14	0.64
Vascular disease	0	25	0	16	--
Allergies	2	23	3	13	0.36
Respiratory disease	4	21	1	15	0.63
Gastroenterological disease	1	24	0	16	1
Cancers	2	23	2	14	0.64
Autoimmune disease	2	23	0	16	0.51
Thyroid disease	2	23	2	14	0.64
Others	4	21	1	15	0.63

p-value (two-sided) obtained from Fisher's exact test for proportions.
**comorbidity history was collected in 25 symptomatic subjects and 16 asymptomatic subjects*
^Some individuals had more than one condition

Table S4. Frequency of medication types in symptomatic and asymptomatic SARS-Cov-2 infected individuals per medication type*

	symptomatic		asymptomatic		
Medication	present	absent	present	absent	p
Ace inhibitors	6	19	2	14	0.45
ARBs	5	20	2	14	0.69
Non-steroideal antiinflammatory drugs (NSAIDs)	1	24	0	16	1
Antihypertensive	13	12	3	13	0.05
Diuretics	3	22	2	14	1
Anticoagulants	1	24	1	15	1
Antiplatelet	2	23	1	15	1
Hypoglycemic	1	24	2	14	0.55
Thyroid hormones	3	22	2	14	1
Other hormones	0	25	1	15	0.39
Immunosuppressants	2	23	0	16	0.51
Corticosteroids	2	23	0	16	0.51
Inhaled drugs	1	24	1	15	1
PPI	1	24	1	15	1
Statins	3	22	2	14	1
Allopurinol	1	24	1	15	1
Other	5	20	2	14	0.69

p-value (two-sided) obtained from Fisher's exact test for proportions.
**medication history was collected in 25 symptomatic subjects and 16 asymptomatic subjects.*

Table S5. Mean and 95% credible interval (CrI) of the parameter estimates obtained with the dynamical model. (pre-symptomatic, symptomatic and asymptomatic infections transmit SARS-CoV-2)**.** Parameter estimates obtained from the fit of the dynamical transmission model described in Extended Data Figure 5 to the observed prevalence of symptomatic, pre-symptomatic and asymptomatic infections in the first and second surveys using the Metropolis-Hastings algorithm.

R_0^1	1/σ	seed	p	1/ν	1/δ	1/γ	1-w	DIC
2.1	2	5.59 (1.96, 17.14)	0.41 (0.32, 0.50)	1.54 (0.01, 5.65)	1.28 (0.47, 2.24)	4.17 (0.65, 5.84)	0.82 (0.67, 0.99)	34.24
2.1	4	6.99 (1.82, 29.62)	0.41 (0.32, 0.50)	2.15 (0.01, 6.05)	1.51 (0.58, 2.76)	3.35 (0.19, 5.58)	0.92 (0.74, 1.00)	32.62
2.1	6	4.04 (1.68, 11.36)	0.41 (0.32, 0.50)	1.31 (0.01, 5.06)	1.91 (0.87, 3.11)	3.78 (0.67, 5.45)	0.95 (0.80, 1.00)	32.41
2.1	8	2.89 (1.51, 7.36)	0.41 (0.31, 0.50)	0.74 (0.01, 4.34)	2.18 (1.09, 3.51)	4.08 (1.24, 5.39)	0.95 (0.82, 1.00)	33.57
2.1	10	2.43 (1.46, 5.56)	0.41 (0.32, 0.51)	0.55 (0.01, 2.99)	2.38 (1.30, 3.74)	4.08 (1.97, 5.30)	0.96 (0.84, 1.00)	34.52
2.1	12	2.23 (1.36, 4.77)	0.41 (0.32, 0.51)	0.48 (0.01, 2.80)	2.45 (1.28, 3.87)	4.08 (2.23, 5.30)	0.97 (0.85, 1.00)	35.39
2.4	2	3.13 (1.03, 9.32)	0.41 (0.32, 0.50)	1.90 (0.04, 6.27)	1.12 (0.39, 2.01)	3.97 (0.34, 5.83)	0.86 (0.74, 0.99)	34.77
2.4	4	3.48 (1.04, 12.32)	0.41 (0.32, 0.50)	2.56 (0.14, 6.11)	1.30 (0.55, 2.34)	3.14 (0.23, 5.45)	0.94 (0.82, 1.00)	33.12
2.4	6	2.25 (1.03, 4.45)	0.41 (0.32, 0.49)	1.83 (0.24, 4.80)	1.59 (0.73, 2.75)	3.58 (1.14, 5.34)	0.96 (0.84, 1.00)	33.38
2.4	8	2.00 (1.03, 4.05)	0.40 (0.31, 0.50)	1.63 (0.29, 4.42)	1.77 (0.88, 3.01)	3.59 (1.10, 5.20)	0.97 (0.87, 1.00)	34.95
2.4	10	1.71 (1.02, 3.23)	0.41 (0.32, 0.50)	1.40 (0.32, 3.82)	1.92 (0.95, 3.17)	3.68 (1.51, 5.17)	0.97 (0.89, 1.00)	36.28
2.4	12	1.55 (1.01, 2.94)	0.41 (0.32, 0.50)	1.25 (0.36, 3.47)	2.02 (1.00, 3.42)	3.73 (1.81, 5.14)	0.98 (0.9, 1.00)	37.52
2.7	2	2.44 (1.05, 5.49)	0.41 (0.31, 0.50)	3.20 (1.00, 6.31)	0.88 (0.37, 1.54)	2.92 (0.22, 5.02)	0.90 (0.79, 1.00)	35.11
2.7	4	2.17 (1.07, 4.63)	0.41 (0.32, 0.50)	3.37 (1.23, 5.85)	1.13 (0.53, 1.97)	2.50 (0.32, 4.60)	0.97 (0.88, 1.00)	32.72
2.7	6	1.77 (1.04, 3.68)	0.41 (0.32, 0.51)	2.91 (1.31, 5.68)	1.33 (0.68, 2.23)	2.76 (0.38, 4.47)	0.98 (0.91, 1.00)	34.26
2.7	8	1.47 (1.01, 2.54)	0.41 (0.31, 0.50)	2.61 (1.36, 4.84)	1.49 (0.75, 2.57)	2.90 (0.86, 4.36)	0.98 (0.92, 1.00)	36.73
2.7	10	1.37 (1.01, 2.54)	0.40 (0.31, 0.50)	2.49 (1.42, 4.66)	1.61 (0.83, 2.79)	2.90 (0.92, 4.29)	0.99 (0.93, 1.00)	38.53
2.7	12	1.33 (1.01, 2.23)	0.41 (0.32, 0.50)	2.50 (1.46, 4.48)	1.67 (0.78, 2.99)	2.83 (0.93, 4.28)	0.99 (0.94, 1.00)	40.40

R_0^1 represents the reproduction number before the implementation of lockdown, $1/\sigma$ represents the average duration of virus detectability beyond the infectious period, seed represents the number of infectious people on 4 February 2020, p represents the proportion of asymptomatic infections, $1/\nu$ represents the average time from infection to virus detectability, $1/\delta$ represents the average time from virus detectability to symptoms onset, $1/\delta + 1/\gamma$ represents the average duration of the infectious period**,** *and* $1 - w$ *represents the reduction in transmissibility after the implementation of lockdown on 24 February 2020. DIC denotes the Deviance Information Criterion.*