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Time between symptom and testing in relation to familial transmission of severe acute respiratory syndrome coronavirus 2

Tempo entre o início dos sintomas e a testagem está relacionado à maior transmissão de SARS-CoV-2 entre contatos familiares

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Abstract *Brazil has a huge number of cases and deaths due to coronavirus disease 2019 (COVID-19); however, few studies have dealt with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among familial contacts in Brazil. Here, we report our findings on transmission in a family-based study in Bauru, São Paulo, Brazil. The study, conducted from July to November 2020, comprised 974 individuals with 233 index patients and 741 familial contacts. Familial contacts were evaluated using the rapid COVID-19 Ag ECO and reverse transcription-polymerase chain reaction (RT-PCR) tests immediately after the index patient diagnosis. The antigen-based rapid test was validated in 121 individuals using RT-PCR as the gold standard. Additionally, 30 days later, familial contacts were evaluated for IgM and IgG antibodies against SARS-CoV-2. We found 333 cases of COVID-19 among familial contacts (44.9%). A positive correlation was observed between the time elapsed from the onset of symptoms until the index patient's COVID-19 testing and the number of family contacts infected by SARS-CoV-2. Early SARS-CoV-2 testing and familial contact evaluation are relevant strategies to contain transmission.*

Key words *COVID-19, SARS-CoV-2, Pandemic*

Resumo *O Brasil apresenta um alto número de casos e óbitos por coronavírus (COVID-19), apesar disso, poucos estudos tratavam da infecção pelo coronavirus-2 causador de síndrome respiratória aguda grave (SARS-CoV-2) entre contatos familiares no Brasil. Relatamos aqui nossos achados sobre a transmissão de SARS-CoV-2 em um estudo de base familiar de Bauru, no estado de São Paulo, Brasil. O estudo foi realizado de julho a novembro de 2020 e compreendeu 974 indivíduos, sendo 233 pacientes índice e 741 contatos familiares. Os contatos familiares foram avaliados por meio do teste rápido COVID-19 Ag ECO Test e RT-PCR imediatamente após o diagnóstico do paciente índice. O uso do teste rápido baseado em antígeno foi validado em 121 indivíduos utilizando RT-PCR como padrão ouro. Adicionalmente, 30 dias após a avaliação inicial, os contatos familiares foram avaliados quanto à presença de anticorpos IgM e IgG contra SARS-CoV-2. Encontramos 333 casos de COVID-19 entre contatos familiares (44,9%). Observamos uma correlação positiva entre o tempo decorrido entre o início dos sintomas e o teste para COVID-19 do paciente índice e o número de contatos familiares infectados por SARS-CoV-2. A testagem precoce da infecção por SARS-CoV-2 e a avaliação de contatos familiares são estratégias relevantes para conter a transmissão.*

Palavras-chave *COVID-19, SARS-CoV-2, Pandemia*

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Introduction

Coronavirus disease 2019 (COVID-19) has brought tremendous challenges to health services. Even with vaccines and promising therapeutics, non-pharmaceutical strategies are essential to control the spread of the virus. The early identification of infected individuals and tracing their contacts are vital steps in controlling the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Studies on transmission risk according to the proximity of familial contacts in China, the United States, and Norway have shown rates of 15.6%, 31%, and 48%, respectively, suggesting that these groups are the most epidemiologically linked clusters[1-3]. Familial contacts are especially vulnerable, considering the limited adoption of protective measures against COVID-19 among these contacts. Despite almost 35 million cases and 690 thousand deaths from COVID-19 in Brazil[4], there are few reports on intrafamilial transmission in our country[5-9].

In this study, we estimated the transmission of COVID-19 among close relatives in a family-based study conducted in a medium-sized city in São Paulo State, Brazil.

Methods

This study included 974 individuals from Bauru, a municipality with approximately 380,000 inhabitants[10], located in the center of São Paulo State, Brazil. The study was approved by the research ethics committee of the Instituto Lauro de Souza Lima (ILSL) (record number 4.474.232) conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants, parents, or guardians, and written assent was obtained from participants younger than 18 years of age.

The patients enrolled in this study were diagnosed with COVID-19 between July and November 2020. Initial medical care and sample collection were conducted in basic health units according to the protocol in force at the time of the study[11]. The molecular diagnosis of COVID-19 by reverse transcription-polymerase chain reaction (RT-PCR) was performed at the ILSL, which is part of a governmental laboratory platform for COVID-19 diagnosis. Immediately after the confirmation of the COVID-19 index case, familial contacts were invited to participate in the study by telephone, regardless of the presence of symptoms. The availability for the call was the only selection criterion. SARS-CoV-2 tests for the volunteers were performed the day after the call.

A total of 233 patients with COVID-19 were diagnosed using RT-PCR (index patients), and 741 familial contacts were evaluated. Sixteen cases were considered as co-prevalent since they presented the first COVID-19 symptoms one day after the index case and were excluded from the analyses. We assumed that all members of the same family unit and close relatives did not necessarily live in the same house had household contact at the time of sickness. According to the public health policies at that time, patients presenting with flu-like symptoms were instructed to wait 4 days from the onset of symptoms before testing for COVID-19. During the study period, the prevalent variants in the southeast region of Brazil were B.1.1.28 and B.1.1.23, and no vaccine was available[12].

A qualitative multiplex assay based on the detection of N, E, and RdRp of SARS-CoV-2 genes was employed for the molecular diagnosis of index patients and symptomatic familial contacts (GeneFinder™ COVID-19 Plus RealAmp OSANG Healthcare Co. Ltd.). The rapid COVID-19 Ag ECO test (Eco Diagnostica Ltda.) was used to test for the presence of the SARS-CoV-2 antigen among familial contacts without symptoms. To validate the use of the ECO test for familial contact diagnosis, we simultaneously performed RT-PCR and rapid tests on 121 individuals.

Thirty days after diagnosis, index patients and familial contacts were invited to take a blood sample to test for IgM and IgG anti-SARS-CoV-2 antibodies using the Hilab rapid test (Hi Technologies Ltd.).

The association of (i) the cycle threshold (Ct) values of RT-PCR, (ii) the age of index patients, and (iii) the interval of time between symptoms and diagnosis of the index patients with the proportion of infected contacts were evaluated using multivariable Poisson regression models in STATA 16 (StataCorp, College Station, TX, USA).

Results

Mean ages were 37.7 (SD 13.5) and 32 years old (SD 20.2), while male/female ratios were 1.95 and 1.17 for index patients and familial contacts, respectively. The mean time for medical evaluation and RT-PCR collection for the index patients was

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4.6 days after the onset of symptoms. The average time between the first symptoms of the index cases and the evaluation of familial contacts was 8.6 days. For all COVID-19 cases, the N gene was detected, while positive results for the E and RdRp genes were reported in 94.0% and 88.0% of the cases, respectively. This is in line with the current literature, showing higher sensitivity for N gene-based assays to detect SARS-CoV-2[13].

Of the familial contacts, 333 (44.9%) out of 741were infected with SARS-CoV-2, considering the results of virus detection (rapid test or RT-PCR) and/or serology. We tested 558 contacts for the presence of the SARS-CoV-2 antigen by rapid testing and obtained 124 positive results (22.2%) (Table 1). For 183 contacts, we used RT-PCR to test for SARS-CoV-2 and found 103 positive results (56.3%). Of the 183 contacts, 140 (76.50%) had common COVID-19 symptoms (fever, headache, lack of taste and smell, sore throat, and others), while in the group tested for SARS-Cov-2 antigen using the rapid test, 386 (69.2%) out of 558, had no symptoms. The IgM and IgG antibodies were evaluated in 556 individuals; 287 (51.6%) presented antibodies against SARS-CoV-2 one month after the initial diagnosis.

The number of days between the first COVID-19 symptom and the day of the RT-PCR test (i.e., the delay in laboratory confirmation) was associated with greater familial contact transmission (IRR=1.06; 95%CI: 1.06-1.16). This indicates that every day of delay in diagnosis was associated with infection in 6% of household contacts. We repeated the Poisson regression model, excluding Ct values and/or age, and obtained similar results. Single Ct values did not influence the results (Table 2).

For the COVID-19 Ag ECO test, the overall sensitivity, specificity, positive predictive value, and negative predictive values were 70.2%, 95.3%, 93.0%, and 78.2%, respectively. The diagnostic accuracy was 83.3%. Positive and negative predictive values are dependent on prevalence and are reported only for this study population. The detailed results are presented in Table 3.

Discussion

Contact tracing is a vital strategy to reduce the incidence of new infectious disease cases. This practice has been adopted for several decades by healthcare entities globally to control the spread of illness. In COVID-19, its purpose is to enable early detection of infected people among individuals exposed to SARS-CoV-2, helping to control transmission[14].

Studies of transmission risk according to the proximity of familial contacts have been performed in China, the United States, Norway, and Brazil. These studies suggest that these groups are the most epidemiologically linked clusters[1-3,15].

We conducted a study in a medium-sized city in the center of São Paulo State with approximately 380.000 inhabitants. Individuals from different neighborhoods and ages were included in this study. Among familial contacts, almost half (44.9%) were infected with SARS-CoV-2. Lugon

Table 1. COVID-19 Ag ECO Test, RT-PCR and serology results from symptomatic and asymptomatic familiar contacts of COVID-19 index patients.

		Symptoms*			Total n (%)
		Symptomatic n (%)	Asymptomatic n (%)	Not reported n (%)	
COVID-19 Ag ECO Test	Positive	66 (39.8%)	57 (14.8%)	1 (16.7%)	124 (22.2%)
	Negative	100 (60.2%)	329 (85.2%)	5 (83.3%)	434 (77.8%)
	Total	166 (29.7%)	386 (69.2%)	6 (1.1%)	558 (100.0%)
RT-PCR SARS-CoV-2	Positive	78 (55.7%)	13 (46.4%)	12 (80.0%)	103 (74.2%)
	Negative	62 (44.3%)	15 (53.6%)	3 (20.0%)	80 (25.8%)
	Total	140 (76.5%)	28 (15.3%)	15 (8.2%)	183 (100.0%)
Serology	Positive	116 (67.4%)	113 (36.9%)	58 (74.4%)	287 (51.6%)
	Negative	56 (32.6%)	193 (63.1%)	20 (25.6%)	269 (48.4%)
	Total	172 (20.8%)	306 (62.8%)	78 (16.4%)	556 (100.0%)

*Presence or absence of symptoms during the first evaluation right after molecular diagnosis of the index patient.

Source: Authors.

Table 2. Multivariable Poisson regression analysis of index case factors associated with greater transmission to households.

Predictor	IRR (95%CI)	p
Age	0.99 (0.98-1.00)	0.09
Days from symptoms to RT-PCR test	1.06 (1.01-1.16)	0.02
CtE	1.02(0.89-1.17)	0.75
CtN	1.02 (0.95-1.09)	0.63
CtR	0.97 (0.86-1.09)	0.58

IRR: Incidence Rate Ratio; CI: Confidence interval; CtE, Cycle Threshold for gene E; CtN, Cycle Threshold for gene N; CtR, Cycle Threshold for gene RdRp.

Source: Authors.

Table 3. Validation of COVID-19 Ag ECO Test versus RT-PCR for COVID-19 diagnosis in 121 individuals.

COVID-19 Ag ECO Test with RT-PCR			
Ag ECO Test	RT-PCR		Total
	Positive	Negative	
Positive	40	3	43
Negative	17	61	78
Total	57	64	121

Sensibility: 70.2%; specificity: 95.3%; positive predictive value: 93.0%; negative predictive value: 78.2%.

Source: Authors.

et al.[7] showed that 77% of intrafamilial transmission was associated with high viral loads (≥1x 10^5 copies of viral RNA per mL of saliva) in a slum in Rio de Janeiro. Similarly, Carvalho *et al.*[15] found that 55.4% (adults) and 37.5% (children) of households of health care workers, a group more exposed to SARS-CoV-2 in São Paulo State, also presented COVID-19.

The first COVID-19 case was confirmed in Bauru on March 30, 2020[16]. By June 2020, the EPICOVID19-BR study, a Brazilian National Seroprevalence Survey, reported that only 0.4% (1 in 250 individuals) of the general population from Bauru had antibodies against SARS-CoV-2[17]. By November 30, 17,930 new COVID-19 cases were confirmed by municipal authorities, representing around 4.7% of the whole city population[18]. Considering that the time of our study (July to November 2020) overlapped with severe government restrictions imposed on the movement of the population, it is reasonable to assume a higher intradomicile transmission than community transmission. This indicates that the findings of the familial transmission of COVID-19 reported here are significant and reliable.

In March 2020, the São Paulo State Government adopted non-pharmaceutical interventions, such as social distancing measures, the use of alcohol gel, and restrictive measures such as shops, restaurants, schools, and public services closures, to contain the SARS-CoV-2 virus infections; however, essential workers had to continue outside activities like working or taking public transportation, leading to exposure to COVID-19 risk. People with acute respiratory illness symptoms were instructed to stay home and wait for at least 3 days after the first symptom before testing for COVID-19. It is important to mention that 95.7% of the cases were of working age (between 15 and 65 years), while only 67.4% of the contacts were in this range. These findings support a positive correlation between the number of days to test for COVID-19 after the onset of symptoms and the number of family contacts infected with SARS-CoV-2. Thus, intrahousehold transmission seems to have been critical at that time.

We can assume that the long time to seek health care delayed the adoption of preventive measures among the families, increasing the transmission of the infection since part of the population had difficulty believing that are infected by SARS-CoV-2 before laboratory confirmation. This fact could have directly impacted elderly people who were instructed to stay home to avoid infection but were vulnerable among close relatives. A study of COVID-19 transmission conducted in India demonstrated that the relative risk of infection by SARS-CoV-2 was 30.9 among household contacts compared with occupational contacts in an open environment[19].

Kuba *et al.*[20] showed that the isolation of index patients within 3 days after the first symptom reduces the secondary infection rate, confirming the value of early diagnosis and distancing to prevent COVID-19 spread, even among familial contacts[20]. In addition, considering the occurrence of pre-symptomatic transmission of SARS-CoV-2, the early diagnosis of COVID-19 is vital to promote the immediate quarantine of household contacts from index patients, contributing to the control of the spread of the virus more than monitoring the occurrence of symptoms[21]. These strategies are critical when more restrictive measures such as lockdown become unviable for socioeconomic reasons, showing

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that the combination of several approaches is necessary[22]. In this context, point-of-care rapid tests for COVID-19 diagnosis are a valuable tool for controlling the spread of the virus. The test manufacturer's data sheet that we evaluated reported a sensitivity of 96.52% and a specificity of >99%. Matsuda *et al.*[23] reported these indexes at 87% and 96%, respectively, when evaluating a population with 97% symptomatic individuals[23]. In our study, among the 121 individuals evaluated, only 81% had symptoms, which may explain the decrease in sensitivity to 70.2% despite 95.3% of specificity. However, we observed a diagnostic accuracy of 83.3%, supporting its use as a good screening test.

This study has some limitations. Household contacts were assumed to all be members of the same family unit, including close relatives who did not necessarily live in the same house. Thus, despite mobility restrictions, we cannot guarantee that infections were not acquired outside the household. In addition, our study was conducted with patients treated in the public health system, most of whom had poor economic conditions. Due to a lack of resources for transportation, the trip to ILSL (15 km from the downtown area) for evaluation became a logistic challenge, and many household contacts withdrew from participating in the study. Finally, these findings are related to the predominant variants at the time of the study (B.1.1.28 and B.1.1.23) and may not reflect the behavior of new variants that emerged after this study.

Conclusion

Here, we describe data that show the impact of early diagnosis as well as the inclusion of household contact investigation as strategies for COVID-19 prevention. Our data reinforce the importance of prioritizing the early diagnosis of people infected by SARS-CoV-2 and promote specific strategies to reduce household transmissions among close relatives. This is especially relevant in the current scenario, where community protection measures have been abandoned in most countries, and new and more aggressive variants of SARS-CoV-2 can still emerge, overriding the protection provided by the current vaccines and natural infection.

Collaborations

ACP Latini, FCS Santana, J Perico, CMCB Fortaleza, VNB Souza and AFF Belone: conception, design and manuscript writing. ACP Latini, FCS Santana, J Perico, BL Martins and DC Menezes: experimental work. ACP Latini, FCS Santana, CMCB Fortaleza, VNB Souza and AFF Belone: data analysis.

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Ethics approval

The study was approved by the Local Ethics Committee (number 4.474.232) and written informed consent was obtained from all participants. All procedures followed were in accordance with the ethical standards of National Commission for Research Ethics (Conep) and the Helsinki Declaration of 1975, as revised in 1983.

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