Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection in household contacts and related factors during the firsts waves of the COVID-19 pandemic in Chile: A longitudinal cohort study

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Highlights

1. Households are the high-risk setting for SARS-CoV-2 transmission.

2. We quantify household secondary attack rate and explore new associated factors with transmission.

3. Prospective longitudinal cohort design, assessing behavioral factors and house structure.

4. Almost half of the household contacts were infected. The composition and structure of the home play an essential role in household SARS-CoV-2 transmission.

Cover letter
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Dear Editor:

We would be most grateful if you could consider for publication in your journal the article "**Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection in household contacts and related factors during the firsts waves of the COVID-19 pandemic in Chile: A longitudinal cohort study**" carried out by our team**.**

This article is **one of very few** that analyzes the role that house structure plays in SARS-CoV-2 transmission and **the first** in suggest that ACE2 levels in oral mucosa may play a role in the transmission of the disease.

We used primary data retrieved by our team in a **prospective longitudinal cohort study with systematic follow up** analyzing the household as the high-risk setting for SARS-CoV-2 transmission, quantifying secondary attack rate and exploring new associated factors with the transmission of the disease, addressing behavioral factors and the house structure among many others.

This manuscript reveals a high rate of household infection during the first wave of the pandemic in Chile and **highlights how the composition and structure of the home play an essential role in household SARS-CoV-2 transmission**. Besides, it suggest an interesting association between ACE2 levels and transmission, which opens up new possible lines of research.

We believe that this manuscript is appropriate for publication in your journal because it addresses aspects of the epidemiology of the disease which are valuable for public health interventions and health policies.

We have not published any related manuscripts or abstracts (included internet) of the submitted paper. All authors of this research paper have participated in the planning, execution, or analysis of this study, and they have read and approved the final version of the submitted manuscript.

There are no conflicts of interest concerning the financial support of the research or the results reported.

We appreciate your consideration!

Sincerely,

XXXXXX XXXXXXXXX
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Abstract

Background

Households are the high-risk setting for SARS-CoV-2 transmission, especially for close and prolonged person-to-person contact. However, the role of household structure and behavioral and clinical factors, especially angiotensin-converting enzyme 2 (ACE2), that contribute to household transmission is scarcely studied. We analyzed the household SARS-CoV-2 infection during the first and second waves of the COVID-19 outbreak and associated factors in household contacts.

Method

We conducted a prospective cohort study of 109 household clusters with a 60-day follow-up (109 index cases and 248 household contacts) in a selected population in Santiago de Chile. Home interviewers measured: symptoms questionnaire, comorbidities, periodontal condition self-report, compliance with non-pharmaceutical interventions, features of household structure and retrieved saliva samples and nasopharyngeal swabs for ACE2 and SARS-CoV-2 viral load determination. The secondary attack rate (SAR) of SARS-CoV-2 risk factors was assessed using Poisson random-mixed models. Incidence rate ratios (IRR) and p-values are reported.

Results

The baseline SAR in household contacts was 0.478 (within household variations of 0.03) and 0.023 (0.001) at the end of the follow-up. Of infected households, 13.6% of contacts were asymptomatic at baseline, 23.7% and 12.7% at 7-day and 14-day follow-up, respectively. Infected household contacts were younger (35.9 y vs. 41.1 y, p=0.02), less hypertensive (9.3% vs. 18.5%, p=0.03), and had lower levels of ACE2 (0.04 ng/dl vs. 0.07 ng/dl, p=0.02) than those uninfected. Factors associated with household transmission were a greater number of adult inhabitants (IRR 0.77. p<0.001) and a greater number of rooms (IRR 0.8, p=.003).

Conclusion

In our study, at the time of index case diagnosis, 47.8% of their household contacts were infected. Meanwhile, at the follow-up only an additional 2.3% were infected. The composition and structure of the home play an essential role in preventing household SARS-CoV-2 transmission. The ACE2 levels may play an important role in household contacts, but further study is needed.

Keywords

Household transmission, SARS-CoV-2, COVID-19, secondary attack rate

Introduction

In March 2020, the World Health Organization declared the coronavirus disease 2019 (COVID-19) outbreak a global pandemic, impacting human health (1). By October 2022, SARS-CoV-2, the virus that causes COVID-19, infected over 623 million people and was responsible for more than 6,5 million deaths worldwide; still, new cases arise every day (2). SARS-CoV-2 vaccination effectively prevents the disease and its severity; however, the virus will continue circulating, and new variants of concern could emerge (3,4). Consequently, it is essential to understand which factors contribute to SARS-CoV-2 transmission for preventive purposes.

The main transmission route of SARS-CoV-2 is the respiratory droplets through close and prolonged person-to-person contact, especially in indoor spaces. Many studies revealed that households are the highest risk setting for virus transmission (5,6), especially in quarantine periods and when new virus variants emerge, with secondary attack rates ranging from 16% to 50% (6,7). A meta-analysis, including 87 studies from 30 countries, reported the age and comorbidities of the household contacts, spousal relationship, and symptomatic status of the index as the main risk factors associated with household transmission (8). However, other relevant variables that could play a role in the virus transmission (e.g., household characteristics, self-care measures, viral load, and ACE2) have been scarcely studied (9-13).

In Chile, from de detection of the first case (march 3, 2020) to September 2021, two COVID-19 outbreaks occurred, and the SARS-CoV-2 B.1.1.7 (Alpha) was the predominant variant. During that time frame this study was conducted.

The aims of this study are to quantify the secondary attack rate of SARS-CoV-2 in households and to explore new factors associated with the transmission of the disease.

Methods

Study design

This study is part of a prospective cohort study of 109 household clusters (109 index cases and 248 household contacts) with a 60 day follow-up. Each household cluster was composited with an index case with SARS-CoV-2 infection confirmed by RT-PCR in nasopharyngeal swabs and at least two household contacts. Index cases were recruited at *Universidad de Los Andes Clinic* and *Davila Clinic* in Santiago, Chile, between October 2020 and September 2021. Eligible contacts were >12 year old for feasibility of saliva sample retrieval, who were permanent residents in the house regardless of family status with index case and who agree to participate. More details of recruitment and measurements were described in previous publication (14).

We measured and recorded clinical variables, comorbidities, symptoms questionnaire, compliance with non-pharmaceutical interventions, household structure features and periodontal condition of index cases and their household contacts. We performed RT-PCR for all household contacts and consequentially calculated the secondary attack rate. We identified risk factors for household transmission and calculate incidence rate ratio (IRR) and p-values.

The project was presented for review and approved by the Ethics Committee of the Davila Clinic, Universidad de Los Andes, and was conducted under the Helsinki Declaration of 1973, as revised in 2003. The study protocol was clearly explained to all the participants who consented to their participation by signing a voluntary informed consent form. In the case of minors, the parents and the minor signed an informed assent form.

Measurements

All subjects were visited at their homes and underwent a clinical interview, symptoms questionnaire and periodontal condition self-report. We recorded compliance with non-pharmaceutical interventions and household structure characteristics. We took saliva samples and nasopharyngeal swabs for ACE2 and SARS-CoV-2 viral load determination.

The secondary attack rate (SAR) of SARS-CoV-2 risk factors was assessed using Poisson random-mixed models. Incidence rate ratios (IRR) were assessed using mixed univariate Poisson regression models and p-values were reported.

We recorded clinical variables (age, gender, body mass index, smoke), patient's history of comorbidities, and symptoms of index cases and their infected household contacts in a predesigned database (Redcap). Paired nasopharyngeal swab samples were also taken from all subjects at the first visit. Besides, we took saliva samples at 7, 14, and 60 days of follow-up and recorded the symptomatology. During the follow-up two cohorts of individuals were identified and compared: infected household contacts, defined as close contacts who tested positive for COVID-19, and uninfected household contacts, defined as those close contacts who remained negative for COVID-19 during the follow up.

Statistical analysis

The categorical variables were described with absolute and relative frequencies. Quantitative variables with statistics of central tendency and dispersion according to the symmetry of their distribution.

Comparison of baseline characteristics differences between infected contacts and uninfected household contacts was assessed using a t-test for paired samples.

The secondary attack rate (SAR) of SARS-CoV-2 risk factors was assessed using Poisson random-mixed models. Incidence Rate Ratios (IRR) and p-values are reported.

The comparison of viral load, basal ACE2, and seven days was carried out through parametric or non-parametric tests for paired samples. It was considered significant at p-values less than 0.05.

The analysis was carried out with the STATA SE V17 Software (Copyright 1985-2017 StataCorp LLC), licensed by the Universidad de Los Andes and with RStudio IDE software (version 2021.9.0.351).

Results

Our study included 109 households with their respective index cases. We identified 248 household contacts, consisting of 118 secondary cases and 130 uninfected household contacts. The mean age of the index cases was 37.48 years and 60 (55.05%) were male.

Table 1 summarizes the baseline characteristics of index cases and household contacts. Overall index cases and infected households contacts shared similar baseline characteristics. There was a greater male proportion in the primary cases (55.05%) than in the secondary cases (40.68%). Compared with uninfected contacts, infected contacts were younger (35.87 vs 41.06, p-value 0.0285) and have a lower hypertension prevalence (table 1).

Regarding non-pharmaceutical interventions, there was a high compliance with mask wearing outside the house, hand washing inside and outside the house and social distancing when outside the house in all three groups. Compliance with mask wearing inside the house was significantly lower than this other measures.

Table 3 summarizes the mixed univariate Poisson model for each variable. Factors associated with household transmission were a greater number of adult inhabitants (IRR 0.766, p<0.001), a greater number of inhabitants per household (IRR 0.857, p=0.005) and a greater number of rooms per hosehold (IRR 0.801, p=0.003). A masculine index case sex might be associate with household transmission although it did not reach statistical significance (IRR 1.449, p=0.05). We did not found a statistically significant association with the index case symptoms (IRR 1.057, p=0.059) or the number of comorbidities (IRR 0.807, p=0.071), nor with any of the other variables studied.

Table 1. Baseline characteristics

	Index case (n=109)	Infected households contacts (n=118)	Uninfected household contact (n=130)	p-value*
Sociodemographic				
Age, mean (sd)	37.48 (12.59)	35.87 (16.04)	41.06 (20.49)	0.0285
Male, n (%)	60 (55.05)	48 (40.68)	64 (49.23)	0.1765
Public health insurance, n (%)	40 (36.7)	48 (40.68)	57 (43.85)	0.700
Education level, n (%)				0.639
University	49 (44.95)	39 (33.05)	42 (32.31)	
Technical studies	23 (21.1)	17 (14.41)	11 (8.46)	
Secondary education	31 (28.44)	41 (34.75)	49 (37.69)	
Primary education	5 (4.59)	18 (15.25)	24 (18.46)	
None	1 (0.42%)	3 (2.54 %)	4 (3.08)	
Preexisting medical conditions				
Hypertension, n (%)	9 (8.26)	11 (9.32)	24 (18.46)	0.0390
Diabetes, n (%)	7 (6.42)	5 (4.24)	9 (6.92)	0.3601
Heart disease, n (%)	4 (3.67)	4 (3.39)	6 (4.62)	0.6241
Cancer, n (%)	4 (3.67)	0 (0)	4 (3.08)	0.0547
COPD, n (%)	1 (0.92)	0 (0)	4 (3.08)	1

CKD, n (%)	0 (0)	0 (0)	6 (4.62)	1
Obesity, n (%)	15 (13.76)	17 (14.41)	18 (13.85)	0.8992
Smoker, n (%)	26 (23.85)	28 (23.73)	24 (18.46)	0.350
Non-pharmaceutical interventions and behaviour				
Compliance with mask wearing inside the house, n (%)	31 (28.44)	22 (18.64)	23 (17.69)	0.8460
Compliance with mask wearing in the street, n (%)	104 (95.41)	112 (94.92)	122 (93.85)	0.7156
Hand washing inside the house, n (%)	101 (92.66)	108 (91.53)	124 (95.38)	0.2167
Hand washing outside the house, n (%)	94 (86.24)	96 (81.36)	106 (81.54)	0.9705
Social distancing (2m) when outside the house, n (%)	91 (83.49)	102 (86.44)	111 (85.38)	0.6827
Goes out for work, n (%)	63 (57.8)	42 (35.59)	39 (30)	0.3482
Goes out for recreation, n (%)	16 (14.68)	23 (19.49)	21 (16.15)	0.4920
Goes out of the city, n (%)	6 (5.5)	2 (1.69)	4 (3.08)	0.4793
Uses public transport, n (%)	21 (19.27)	14 (11.86)	15 (11.54)	0.9364
Social gatherings with people from outside the house, n (%)	6 (5.5)	5 (4.24)	7 (5.38)	0.6741
Oral Health				
Gingivitis, n (%)	24 (22.02)	18 (15.25)	26 (20)	0.3286
Periodontitis, n (%)	39 (35.78)	34 (28.81)	42 (32.31)	0.5511
Enfermedad periodontal, n (%)	56 (51.38)	41 (34.75)	59 (45.38)	0.0881
ACE2 expression, n (%)	49 (44.95)	68 (57.63)	27 (20.77)	0.4120
Laboratory exams				
ACE-2 (ng/mL), mean	0.0259	0.0375	0.0699	0.0213

*p-value compares differences between the distribution of infected versus uninfected household contacts.

Table 2. Household characteristics of the primary cases and household contact characteristics

	Mean (min-max)
Number of rooms	3.6 (1-7)
Number of inhabitants	4.8 (2-9)
Number of adults inhabitants	3.5 (1-6)
Number of child inhabitants	0.4 (0-4)
Number of household contacts per case	2.2 (1-7)
Total household contacts	248
Number of infected household contacts	118
Household infected proportion* (sd)	0.478 (0.03)

*Mixed models

Table 3. IRR of SARS-CoV-2 infection in household contacts: mixed univariate Poisson models

	IRR (CI 95%)	p-value
Sociodemographic		
Index case sex	1.449 (0.999 - 2.101)	0.050
Sex	0.833 (0.577 - 1.202)	0.328
Index case age	1.004 (0.990 - 1.017)	0.604
Age	0.992 (0.982 - 1.002)	0.113
Index case educational level	1.110 (0.905 - 1.361)	0.315
Educational level	1.044 (0.897 - 1.217)	0.575
Index case health insurance	0.985 (0.664 - 1.461)	0.940
Health insurance	0.934 (0.647 - 1.348)	0.715
Hosehold characteristics		
Number of adults in household	0.766 (0.664 - 0.884)	< 0.001*
Number of children in household	0.955 (0.711 - 1.282)	0.758
Number of persons per room	1.120 (0.821 - 1.527)	0.476
Number of persons per household	0.857 (0.770 - 0.954)	0.005*
Number of rooms per household	0.801 (0.693 - 0.925)	0.003*
Clinical		
Number of comorbidities	0.807 (0.639 - 1.018)	0.071
Index case symptoms	1.057 (0.998 - 1.120)	0.059
Non-pharmaceutical interventions and behaviour		
Compliance with mask wearing inside the house	0.996 (0.832 - 1.194)	0.970
Compliance with mask wearing in the street	1.004 (0.715 - 1.409)	0.982
Hand washing inside the house	0.845 (0.638 - 1.119)	0.241
Hand washing outside the house	0.997 (0.824 - 1.206)	0.973
Social distancing (2m) when outside	1.047 (0.839 - 1.306)	0.685

the house		
Goes out for work	1.066 (0.920 - 1.235)	0.396
Goes out for recreation	1.061 (0.870 - 1.295)	0.557
Goes out of the city	1.217 (0.881 - 1.680)	0.234
Uses public transport	1.021 (0.827 - 1.261)	0.843
Social gatherings with people from outside the house	1.094 (0.810 - 1.478)	0.556
Oral Health		
Gingivitis	0.834 (0.504 - 1.379)	0.480
Periodontitis	0.916 (0.615 - 1.364)	0.666
Enfermedad periodontal	0.788 (0.539 - 1.151)	0.218
Laboratory exams		
Index case viral load	0.999 (0.99998 - 1.00001)	0.687
Index case ACE 2 level	0.809 (0.020 - 32.141)	0.910
ACE 2 level	0.165 (0.008 - 3.325)	0.240
ACE2 expression	0.923 (0.633 - 1.345)	0.675

Discussion

In our study, conducted during the first wave of the pandemic in Chile, almost half of the contacts were infected by the index case (secondary attack rate 47.8%). There is great variability in the SAR of the first wave in the different countries ranging between 16% to 50%, our rate is in the upper part of that range. Considering that at the time of the pandemic in Chile, quarantine measures were very rigid and there were multiple traceability and surveillance programs implemented, it is remarkable the high rate of secondary infection. This could have relation with sociocultural factors of Chilean society and with the low compliance of the use of face mask inside the house.

Overall, compliance of non pharmaceutical interventions was relatively high. Our study showed a greater compliance than others published before (15), although this did not associated significantly with transmission inside the household which could be due to the low potency of our study.

The associated factors found in this study are directly linked to the structure of the house itself. However, this has been scarcely studied in the literature. Unlike previous studies, we did not find a significant association with viral load levels and the transmission of COVID-19. However, there were significant differences in ACE 2 levels between infected and uninfected contacts, which deserve to be further explored in more powerful studies. After all this receptor has been identified as the key receptor for viral entry into the cell, being the place where the receptor binding domain of SARS-CoV-2 binds (16).

We identified a greater number of adult inhabitants and a greater number of rooms as key factors in SARS-CoV-2 transmission. This has been scarcely reported in literature, and others studies have failed in show a relation between house structure and transmission (17).

The strengths of our study are its longitudinal nature and the systematic follow-up of family clusters, which provides valuable primary information on the evolution of the disease in the family. It is also worth mentioning that all the diagnoses considered for the study were cases confirmed with RT-PCR, carried out in certified laboratories, which at that time of the pandemic in the world was not an easy task. Finally, it is important to highlight that a good number of participants were recruited considering the prospective nature of the study and the fact that it was carried out during the first wave of the pandemic.

On the other hand, within the limitations of the study we can mention that it lacks population representativeness as it is a selected sample, the method used does not allow the exact determination of basal contagion (small latency between index case diagnosis and infected contact diagnosis) and the sample size lacks of power to evaluate all the proposed associations.

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