Transmission of COVID-19 in 282 clusters in Catalonia, Spain: a cohort study

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ABSTRACT

Background

There remains limited data on what variables affect the risk of transmission of SARS-CoV-2 and developing symptomatic Covid-19 and in particular the relationship to viral load (VL).

Methods

We analysed data collected in a trial of hydroxychloroquine post-exposure prophylaxis. Covid-19 cases and their contacts were identified through the local epidemiological surveillance system. VL, estimated by quantitative PCR, was assessed at enrollment, at day 14, and whenever the participant reported Covid-19-like symptoms. Risk of transmission, risk of developing symptomatic disease and incubation dynamics were evaluated using random-effects regression analysis.

Findings

We identified 314 cases, 282 of which had at least one contact (753 contacts in total). Ninety (33%) of 282 clusters had at least one transmission event. The secondary attack rate was 16% (125/753), with a variation from 12% to 24% for VL of the index case of $<10^6$, and $>10^9$ copies/mL, respectively (OR per $\log_{10}$ increase in VL 1.3 95%CI 1.1–1.6). Increased risk of transmission was also associated with household contact (OR 2.7; 1.4–5.06) and age of the contact (OR 1.02; 1.01–1.04). The proportion of PCR positive contacts who developed symptomatic Covid-19 was 40.3% (181/449), with a variation from 25% to 60% for VL of the contact $<10^7$, and $>10^9$ copies/mL (HR $\log_{10}$ increase in VL 1.12; 95% CI 1.05 – 1.2). Time to onset of symptomatic disease decreased from a median of 7 days (IQR 5–10) for individuals with an initial viral load $<10^7$ to 6 days (4–8) and 5 days (3–8) for individuals with an initial viral load of 10^7–10^9 and $>10^9$, respectively.

Interpretation

We show that the viral load of the index case is a leading driver of SARS-CoV-2 transmission. The risk of symptomatic Covid-19 is strongly associated with viral load of the contact at baseline, which shortens the incubation time in a dose-dependent manner.

Funding: Crowdfunding campaign YoMeCorono (https://www.yomecorono.com/), and Generalitat de Catalunya.

Research in context

Evidence before this study

In September 2020, we searched PubMed database for articles reporting on factors influencing transmission and the risk of developing symptomatic disease. Search terms included "Covid-19", "transmission", "incubation time", and "risk", with no language restrictions. By the time of performing this search, various authors had reported on retrospective analyses of clusters of index cases and their corresponding contacts, as well as series of patients who developed symptomatic Covid-19 disease after PCR positive result. Besides describing the secondary attack rate, various authors identified risk factors for transmission associated with the place and duration of exposure and the lack of use of personal protective equipment. However, we found no clear evidence regarding the influence of the characteristics of the index case on transmission risk. Similarly, although various retrospective series of patients with positive PCR results had reported incubation times elsewhere, the characteristics of index case and contacts that may influence the risk of developing symptomatic Covid-19 and the time to this event had been barely addressed.

Added value of this study

We analyzed data from a large cluster-randomized clinical trial on post-exposure therapy for Covid-19 that provide new information on SARS-CoV-2 transmission dynamics. Several design components add value to this dataset. Notably, quantitative PCR was available for the index cases to estimate risk of transmission. Furthermore, quantitative PCR was also performed on asymptomatic contacts at the time of enrollment allowing to investigate the dynamics of symptomatic disease onset among them. We found that the viral load of the index case was the leading determinant of the risk of SARS-CoV-2 PCR positivity among contacts. Among contacts who were SARS-CoV-2 PCR positive at baseline, viral load significantly influenced the risk of developing the symptomatic disease in a dose-dependent manner. This influence also became apparent in the incubation time, which shortened with increasing baseline viral loads.

Implication of all the available evidence

Our results provide important insights into the knowledge regarding the risk of SARS-CoV-2 transmission and Covid-19 development. The fact that the transmission risk is primarily driven by the viral load of index cases, more than other factors such as their symptoms or age, suggests that all cases should be considered potential transmitters irrespective of their presentation and encourages assessing viral load in cases with a larger number of close contacts. Similarly, our results regarding the risk and

expected time to developing symptomatic Covid-19 encourage risk stratification of newly diagnosed SARS-CoV-2 infections based on the initial viral load.

INTRODUCTION

According to current evidence, Covid-19 is primarily transmitted from person to person through respiratory droplets, as well as indirect contact, through transfer of the virus from contaminated fomites to the mouth, nose, or eyes.[1,2] Several outbreak investigation reports have shown that Covid-19 transmission can be particularly effective in confined indoor spaces such as workplaces including factories, churches, restaurants, shopping centers, or healthcare settings.[3–6] In Spain, and many other countries, healthcare workers have experienced a high rate of Covid-19 infection.[7]

The availability of data regarding the factors that may enhance transmission is essential for designing interventions to control SARS-CoV-2 spread. Currently available data provide information on the risk of transmission related to the place and duration of exposure, and the use of respiratory and eye protection[1,3–5,8] but not on other factors related to the characteristics of index cases and their contacts. Over the course of infection, the virus has been identified in respiratory tract specimens 1–2 days before the onset of symptoms, and it can persist for up to 13 days after the onset of symptoms in mild cases.[9] However, the detection of viral RNA by PCR does not necessarily equate with infectivity, and the exact relationship between viral load and risk of transmission from a case is still not clear.[10,11]

Another challenge for public health interventions is the risk stratification of infected individuals for developing symptomatic illness. Studies investigating case-contact pairs have reported highly variable secondary attack rates (i.e., range 0.7% to 75%), depending on the type of exposure—duration, place, pre- or post-symptomatic.[12–15] On the other hand, the proportion of PCR-positive infected contacts that progress to symptomatic disease has been typically around 40% – 60%.[16] Estimates of mean or median incubation period have been consistently between 5–7 days.[17–19] Nonetheless, little is known about factors that may contribute to variation on the risk of developing Covid-19 symptoms or the incubation periods among infected individuals.

The objective of this study was to evaluate transmission dynamics of SARS-CoV-2 in the context of a trial of post-exposure prophylaxis and evaluate the influence of baseline variables—including viral load of the index cases and exposed contacts—to transmission, development of symptomatic disease, and the incubation period.

METHODS

Study design and participants

This was a post-hoc analysis of data collected in the BCN PEP CoV-2 Study (NCT04304053), a cluster-randomized trial that included PCR-confirmed Covid-19 cases and their close contacts occurred between Mar 17 to Apr 28, 2020, during the SARS-CoV-2 outbreak, in three out of nine healthcare areas in Catalonia (North-East Spain): *Catalunya central, Àmbit Metropolità Nord, and Barcelona Ciutat*, total target population 4,206,440 people. The study protocol of the BCN PEP CoV-2 Study was approved by the ethics committee of Hospital Germans Trias Pujol, (Badalona, Spain). Written informed consent was obtained from all participants. Full details of the original study are reported elsewhere.[20]

Covid-19 cases were identified using the electronic registry of the Epidemiological Surveillance Emergency Service of Catalonia (SUVEC) of the Department of Health.[21] Following government ordinance, the SUVEC registered all new Covid-19 diagnoses occurred from March 16, 2020. The surveillance system included active tracing of all contacts with recent history of exposure, defined as being in contact with a SARS-CoV-2 PCR positive case during more than 15 minutes within two meters.

All Covid-19 cases included in the present analysis were non-hospitalized adults (i.e., ≥ 18 years of age) with quantitative PCR result available at baseline, mild symptom onset within five days before enrollment, and no evidence of SARS-CoV-2 infections in their accommodation (i.e., household or nursing home) or workplace within the 14 days before enrollment. Contacts selected for the analysis were adults with a recent history of exposure and absence of Covid-19-like symptoms within the seven days preceding enrolment. Contacts were exposed to the index case as either a healthcare worker, a household contact, a nursing home worker, or a nursing home resident.

Study procedures and data collection

A dedicated outbreak field team visited cases and contacts at home or nursing home on days 1 (enrollment) and 14. At the first clinical assessment on day 1 they conducted a baseline assessment, including a questionnaire for symptoms of Covid-19 and collected relevant epidemiological information using a structured interview: time of first exposure to the index case, place of contact (hospital, home, nursing care facility), routine use of a mask of both, the case and the contact, and sleep location concerning the index case (e.g., same room, same house). Symptoms surveillance consisted of active monitoring by phone on days 3, and 7, a home visit on day 14, and passive monitoring whenever the participants developed symptoms. Participants who developed symptoms were visited the same day they

notified symptom onset (unscheduled visits) by the field team, which recorded the date of symptom onset, type of symptoms from a pre-specified checklist, and symptom severity, graded on a 1-to-4 scale.

Serial SARS-CoV-2 PCR test and viral load titration on nasopharyngeal swab were conducted on day 1 and day 14 to all participants, and on any unscheduled visit when the participant notified the onset of Covid-19 symptoms. The detection of the SARS-CoV-2 virus was performed from nasopharyngeal swabs at SYNLAB Diagnostics (Barcelona, Spain) by PCR using TaqMan™ 2019-nCoV Assay Kit according to the manufacturer's protocol (Catalog number: A47532, Thermo Fischer Scientific Inc.). Viral load was quantified from nasopharyngeal swabs at IrsiCaixa laboratory (Badalona, Spain) by PCR amplification, based on the 2019-Novel Coronavirus Real-Time RT-PCR Diagnostic Panel guidelines and protocol developed by the American Center for Disease Control and Prevention (CDC).[22] For absolute quantification, a standard curve was built using 1/5 serial dilutions of a SARS-CoV2 plasmid (2019-nCoV_N_Positive Control, catalog no. 10006625, $2x10^5$ copies/µL, Integrated DNA Technologies) and run in parallel to all PCR determinations.

Outcomes and definitions

Transmission was characterized by examining the number of infected and uninfected individuals among close contacts to an index case. We defined transmission events as PCR-positivity at any time point (i.e., days 1, 14, or at any other unscheduled PCR testing when participants referred symptoms) of a contact in the same household or workplace within the 14 days following enrollment. Following the WHO guidelines, we defined the secondary attack rate as the ratio of PCR-positive individuals among close contacts.

The exposure time was defined as the time from the earliest possible contact with the symptomatic index case, based on individual contact investigation. The incubation period was defined as time from first exposure to symptom onset, with later confirmation of infection by PCR.[23]

Statistical Analysis

The relationship between clinical and demographic characteristics of cases and their viral load was assessed using linear regression and included all Covid-19 cases, regardless of the presence or not of close contacts. The analysis regarding the determinants of transmission was performed using clusters of an index case (i.e., a Covid-19 case with at least one close contact) and their corresponding contacts. To identify risk factors for transmission, we fitted a random-effects logistic regression model for the risk of transmission within a cluster. Factors with potential influence on the risk of transmission included characteristics of the potential transmitter (i.e., age, sex, viral load, and the presence or absence of

respiratory symptoms) and contacts (i.e., age, sex, and the type of contact they had with the index case). Finally, the analysis regarding the risk of developing symptomatic Covid-19 included all contacts with positive PCR result at baseline, irrespective of the characteristics and available data of the index case. We assessed the time from exposure to development of symptomatic disease and fitted a cox-regression model to explore the factors that may influence it. Data at 14 days after the first study visit were censored, in line with the follow-up conducted in the original trial. All analyses were conducted in R version 4.0.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Population characteristics

During the investigation period, we identified 314 cases in whom the viral load was tested. Overall, 220 (70.0%) were female and the median age was 41 (IQR 31-52). Of them, 282 had at least one close contact, resulting in the corresponding clusters, with a total of 753 contacts. Clusters had a median of 2 contacts (IQR 1-3) and a maximum of 19 contacts. Most index cases of the clusters were female (n= 202, 71.6%), with an average age of 42 years (SD 13 years) (Table 1).

Index case viral load

At the first study visit, the median viral load amongst Covid-19 cases was 10^8 (IQR 10^6-10^9). In multivariable linear regression the viral load amongst cases was higher in individuals who reported cough, fever, or rhinitis (Table 2). There was no association between the age or sex of the Covid-19 case nor the presence of reported dyspnea or anosmia with viral load.

Cluster-level transmission

For our risk factor analysis on SARS-CoV-2 transmission we used linked case and contact data of 282 clusters with 753 contacts. At the cluster level, 90 (33.3%) of the 282 clusters had at least one transmission event, with a highly skewed distribution of the number of transmission events per cluster (Figure 1A). A total of 125 (16.6%) of 753 contacts had a PCR positive result over the study period. The proportion of contacts who tested positive for SARS-CoV-2 within a cluster (secondary attack rate) progressively increased with the viral load of the index case: from 12% where the index case had a viral load of $<10^6$ copies/mL to 24% where the index case had a viral load $>10^9$ copies/mL (Figure 1B).

According to the multivariate analysis, the viral load of the index case was strongly associated with the risk of onward transmission (OR per $\log_{10}$ increase in VL 1.3; 95% CI 1.1-1.6) (Table 3). Ninety percent (114/125) of transmission events had an index case viral load of 5.1 $\log_{10}$ copies/ml or more, and 50% (61/125) had a viral load of 8.8 $\log_{10}$ copies/ml or more. Other factors associated with an increased risk of transmission were household contact (OR 2.7, 95% 1.4-5.06) and age of the contact (OR 1.02, 95% 1.01-1.04). There was no association of risk of transmission with reported mask usage by contacts, with the age or gender of the index case nor with the presence of respiratory symptoms in the index case at the initial study visit (Table 3).

We did not find any evidence of an association between the viral load of the index cases and the first viral load of incident positive results amongst contacts (p = 0.1, Supplementary Figure 1). Also, after excluding contacts who were PCR positive at the first study visit, we found no association between the viral load of the index case and the time to onset of incident SARS-CoV-2 infection (HR 1.01 95% CI 0.83-1.23).

Risk factor for Covid-19 disease among PCR+ contacts

Overall, 449 contacts had a positive PCR result at first visit regardless of availability on viral load data of their index case (n=125) or not (n=324). Twenty-eight (6.3%) of 449 contacts had symptoms at the first visit and 181 (40.3%) developed symptomatic Covid-19 within the follow-up period. The multivariable cox-regression analysis, after adjusting for age and sex, revealed that increasing viral load levels of the contact at day 1 were associated with an increased risk of developing symptomatic disease. The risk of symptomatic disease was approximately 25% amongst individuals with an initial viral load of $<10^7$ copies/mL compared to a more than 60% amongst those with an initial viral load of $>10^9$ (HR per $\log_{10}$ increase in VL 1.12; 95% CI 1.05 – 1.2; p = 0.0006) (Figure 2A). There was no association between with sex or age of individuals and the risk of developing symptomatic Covid-19.

The median time from exposure to symptom onset was 7 days (IQR 5 – 9). The time to onset of symptomatic disease decreased from a median of 7 days (IQR 5 – 10) for individuals with an initial viral load $<10^7$ copies/mL to 6 days (IQR 4 – 8) and 5 days (IQR 3 – 8) for individuals with an initial viral load of 10^7-10^9 and $>10^9$ copies/mL, respectively (Figure 2B). Overall, 110/181 (60.8%) of participants became symptomatic before day 8, 45/181 (24.9%) between days 8-10, and 22/181 (12.2%) between days 11-14.

DISCUSSION

In our study, we found that increasing viral load values in nasopharyngeal swabs of Covid-19 cases were associated with the greatest risk of transmission measured by SARS-CoV-2 PCR positivity among contacts and also a higher risk of transmission in household environment compared to other indoor situations. In addition, we found that higher viral loads in swabs of asymptomatic contacts were associated to higher risk of developing symptomatic Covid-19 and have shorter incubation periods than those with a lower viral load.

To our knowledge this is the largest study that evaluates the relationship of viral load in Covid-19 cases and risk of transmission. In our cohort, a high proportion (67%) of index cases did not cause secondary infections. However, we identified 90 (33%) clusters with transmission events and the multivariate analysis revealed that clusters centered on index cases with high viral load were significantly more likely to result in transmission. Secondary attack rate was under 12% when the index case viral load was $<10^6$ copies/ml compared to more than 20% amongst clusters with the highest viral loads. In line with previous analyses of case-contact clusters,[9,12,14] we also found that household exposure to an index case was associated with a higher risk of transmission that other types of contact, presumably reflecting duration and proximity of exposure. Age of the contact was also identified in our multivariate analysis as a significant—albeit modest—determinant of transmission. This factor has shown uneven influence across results reported elsewhere, but seems to play a secondary role among adults.[13,14] Finally, unlike previous analyses that reported a relationship between coughing and transmission,[13] we did not find any association. This finding suggests that the absence of cough does not preclude significant onward transmission, particularly if the viral load is high. Taken together, our results indicate that the viral load, rather than symptoms, may be the predominant driver of transmission.

Importantly, we report that high viral short after exposure in asymptomatic contacts was strongly associated with the risk of developing symptomatic Covid-19 disease. We found an approximately 25% chance of developing symptomatic disease amongst individuals with an initial viral load $<10^7$ copies/mL compared to a more than 60% chance amongst individuals with a viral load $>10^9$. These data may provide rationale for risk stratification for developing illness. Moreover, the initial viral load significantly shifted the incubation time, which ranged from 5 days in participants with a high viral load to 7 days in participants with a low viral load. Our study is the first analysis of prospective data that investigates the association between initial viral load and the incubation time.

The study has several limitations. First, asymptomatic people were not enrolled as index cases, affecting our ability to fully characterize all types of transmission chain. Second, we did not find any evidence of

decreased risk of transmission in individuals who reported mask use. While this finding collides with the evidence reported elsewhere,[8] we did not have fine-grained data on type of mask (surgical vs FFP2), use of other measures of PPE or other infection control practices, thus limiting our ability to make clear inferences about the impact of PPE on transmission risk. Third, we used time to symptom onset (with later confirmation of infection) rather than time to positive PCR test based on serial testing. Nonetheless, accurate calculation of the incubation period was feasible because of the prospective nature of the study, accurate identification of exposure by face-to-face interview, and intensive active and passive monitoring of exposed contacts. Also, we followed participants over 14-day periods, thus incubation periods beyond 14 days may not have been detected.

In summary, our results provide evidence regarding the determinants of SARS-CoV-2 transmission, particularly on the role of the viral load. The higher risk of transmission among individuals with higher viral loads adds to current evidence and encourages assessing viral load in cases with a larger number of close contacts. When a case with high viral load is identified, implementation of reinforced contact tracing measures and quarantines, may be critical to reduce onward transmission. Similarly, our results regarding the risk and expected time to developing symptomatic Covid-19 encourage risk stratification of newly diagnosed SARS-CoV-2 infections based on the initial viral load.

CONTRIBUTORS

CONFLICTS OF INTEREST

We declare no conflicts of interest

ACKNOWLEDGMENTS

The authors would like to thank Gerard Carot-Sans for providing medical writing support during the preparation of the manuscript.

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Tables

Table 1:

Baseline Characteristics of linked transmission clusters

Cluster Size	Median (IQR)	2 (1-3)
Index Case Age	Years – Mean (SD)	42 (13)
Index Case Sex	Female	202
Index Case Log Viral Load	Median (IQR)	8 (6-9)
Contacts Age	Years – Mean (SD)	42 (15)
Contacts Gender	Female	385
	Male	205
	Missing	63
Baseline PCR of Contact Case	Positive	93
Contact	HCW	254
	Household	382
	Nursing Home	21
	Unknown	96

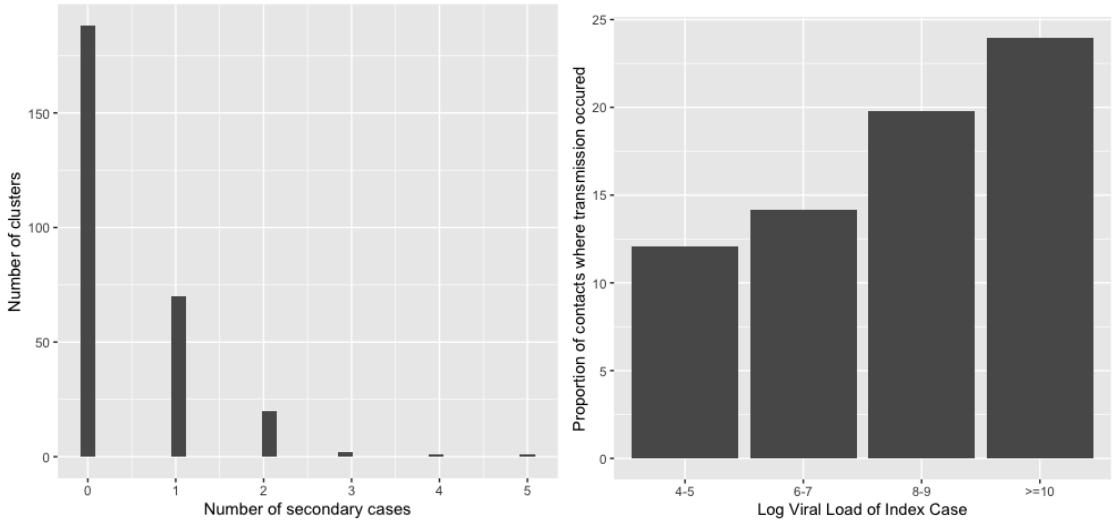
Table 2: Univariate and multivariate linear regression of association between Index case variables and log_{10} viral load

Characteristic		Log_{10} Viral Load/ml	Unadjusted β coefficient (95% CI)	p	Adjusted β coefficient (95% CI)	p
Case Age		N/A	0.002 (-0.02 – 0.02)	0.78	0.005 (-0.01 – 0.02)	0.55
Case Sex	Male	8.15 (7.54 – 8.77)	Reference		Reference	
	Female	8.04 (7.47 – 8.6)	-0.238 (-0.72 – 2.4)	0.33	-0.12 (-0.60 – 0.36)	0.63
Cough	Absent	7.82 (7.24 – 8.41)	Reference		Reference	
	Present	8.37 (7.78 – 8.95)	0.66 (0.22 – 1.1)	0.003	0.55 (0.11 – 0.99)	0.02
Dyspnea	Absent	7.97 (7.5-8.43)	Reference		Reference	
	Present	8.22 (7.45-8.99(	0.27 (-0.40 – 0.94)	0.42	0.26 (-0.41 – 0.92)	0.45
Fever	Absent	7.77 (7.16 – 8.38)	Reference		Reference	
	Present	8.42 (7.86-8.98)	0.80 (0.36 – 1.24)	0.0004	0.64 (0.20 – 1.09)	0.005
Anosmia	Absent	8.32 (7.76 – 8.88)	Reference		Reference	
	Present	7.87 (7.25-8.49)	-0.57 (-1.0 - -0.09)	0.02	-0.45 (-0.92 – 0.02)	0.06
Rhinits	Absent	7.60 (7.23 – 7.98)	Reference		Reference	
	Present	8.59 (7.65-9.52)	0.88 (-0.05 – 1.82)	0.06	0.98 (0.06 – 1.91)	0.04

Table 3: Risk factors for transmission of SARS-CoV-2

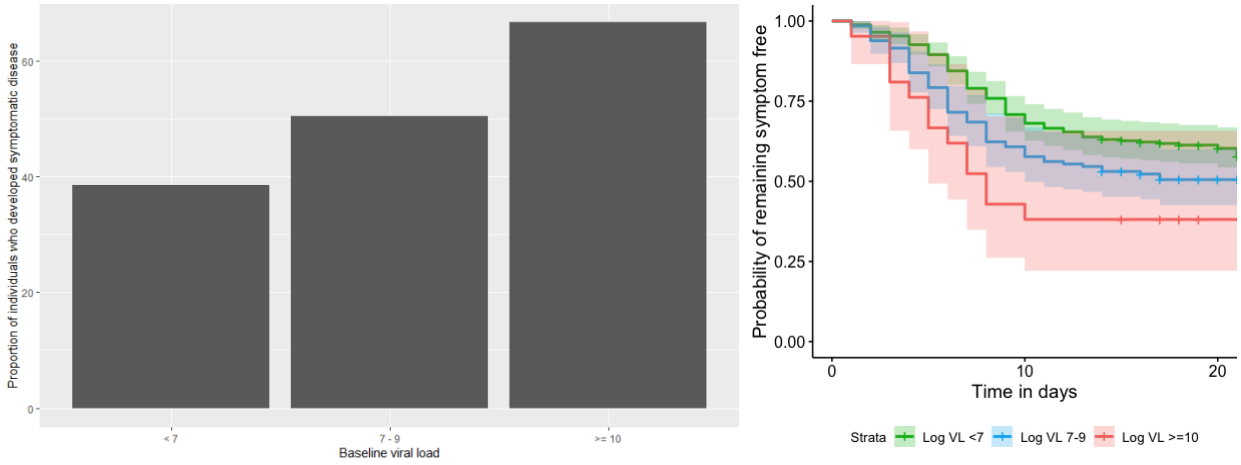
		Unadjusted Odds Ratio	**Confidence Interval**	**p**	**Adjusted Odds Ratio**	**Confidence Interval**	**p**
Index case age (per year)		1.02	0.99-1.05	0.07	1	0.99-1.03	0.46
Female Index Case		0.74	0.4-1.36	0.33	0.66	0.35-1.25	0.21
Index Case Viral Load (per Log_{10} change)		1.27	1.09-1.48	<0.01	1.3	1.1-1.5	<0.01
Index Case Cough		1.0	0.55-1.82	0.99	1.1	0.69 – 2.2	0.45
Index Case Dyspnea		0.80	0.31-2.07	0.64	0.76	0.3 – 1.9	0.58
Age of Contact		1.03	1.01-1.05	<0.01	1.02	1.01 – 1.04	<0.01
Female Contact		0.93	0.58-1.49	0.77	1.25	0.7 – 2.1	0.4
Mask Use	Never	1 (Reference Group)	N/A	N/A	1 (Reference Group)	N/A	N/A
	Always	0.93	0.47 – 1.83	0.84	1.51	0.73 – 3.31	0.27
	Unknown	1.18	0.59 – 2.36	0.47	1.47	0.71-3.02	0.30
Contact Type	Healthcare Work	1 (Reference Group)	N/A	N/A	1 (Reference Group)	N/A	N/A
	Household	3.07	1.68-5.62	<0.01	2.7	1.4 – 5.06	<0.01
	Nursing Home	1.75	0.19 -16.01	0.62	2.06	0.26 – 16.6	0.5
	Other	0.32	0.03-3.05	0.32	0.49	0.04 – 5.5	0.57

Figure 1: Transmission in a cluster



(A) Number of secondary cases per cluster. (B) Relationship between viral load of the index case and the proportion of contacts developing Covid-19. Numbers 18/149 in group 10^4-10^5 RNA copies/ml; 30/2012 in group 10^6-10^7; 59/298 in group 10^8-10^9; 17/71 in group $\geq 10^{10}$.

Figure 2. Risk of developing symptomatic Covid-19 according to characteristics of the contact at enrolment.



(A) probability of symptomatic disease by viral load. (B) time to symptomatic disease by viral load.

Supplementary Figure 1: Relationship between Index Case and Contacts Viral Load

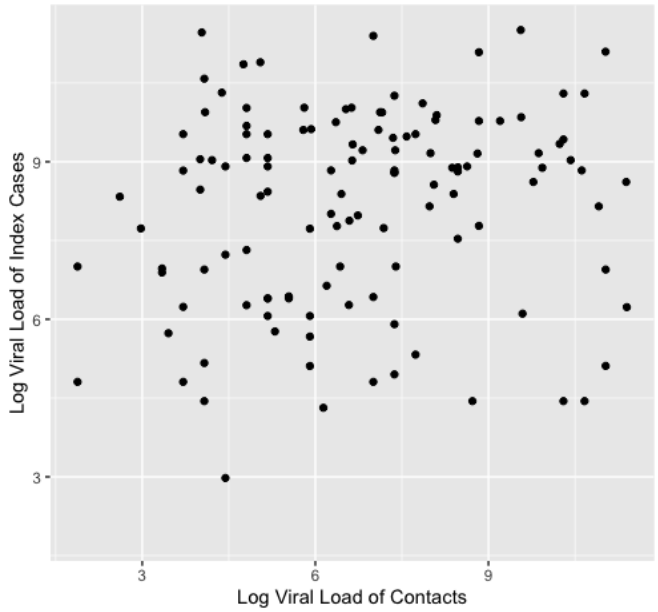


Figure 1A

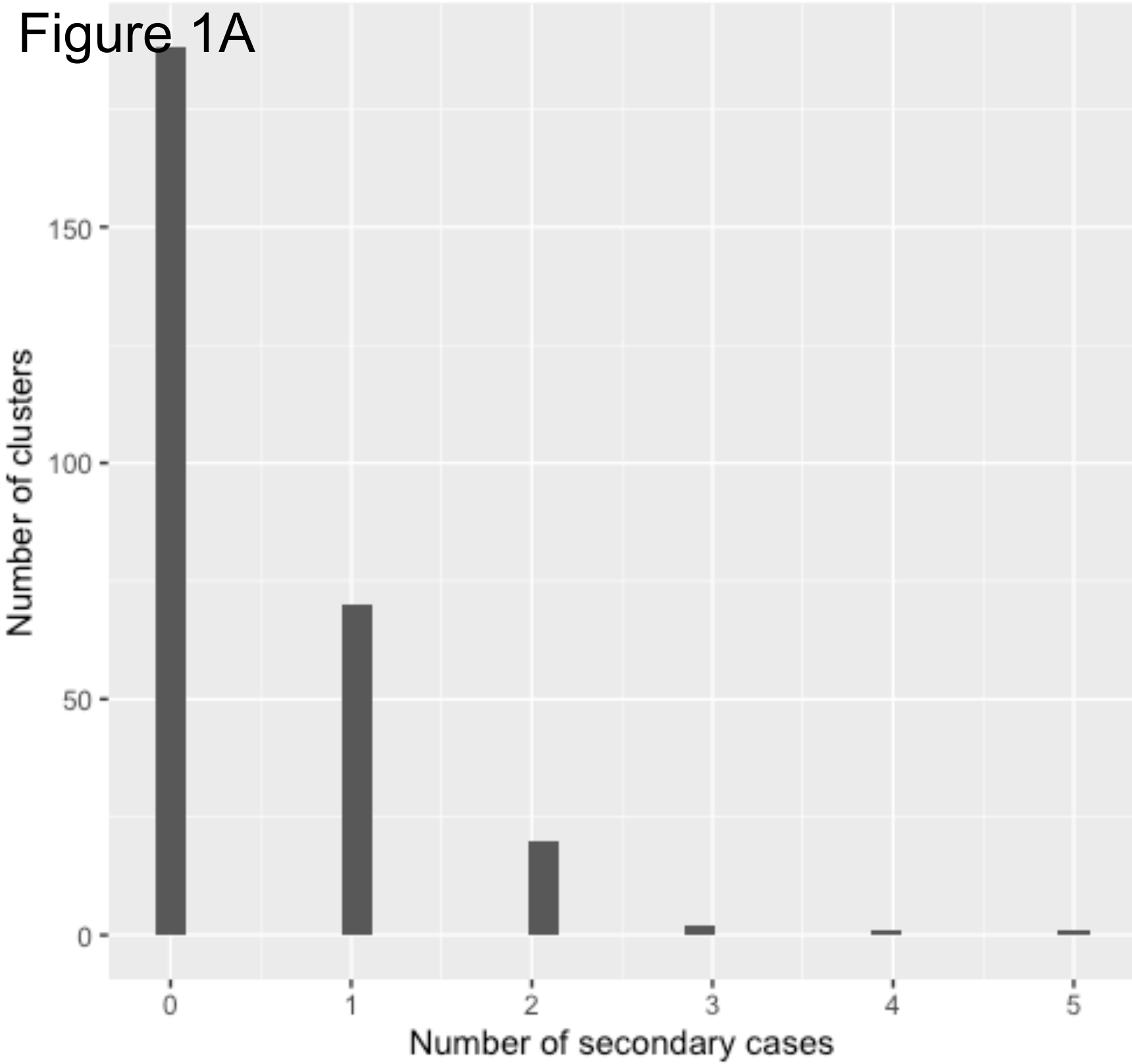

Number of clusters
150
100
50
0
0
1
2
3
4
5
Number of secondary cases

Figure 1B

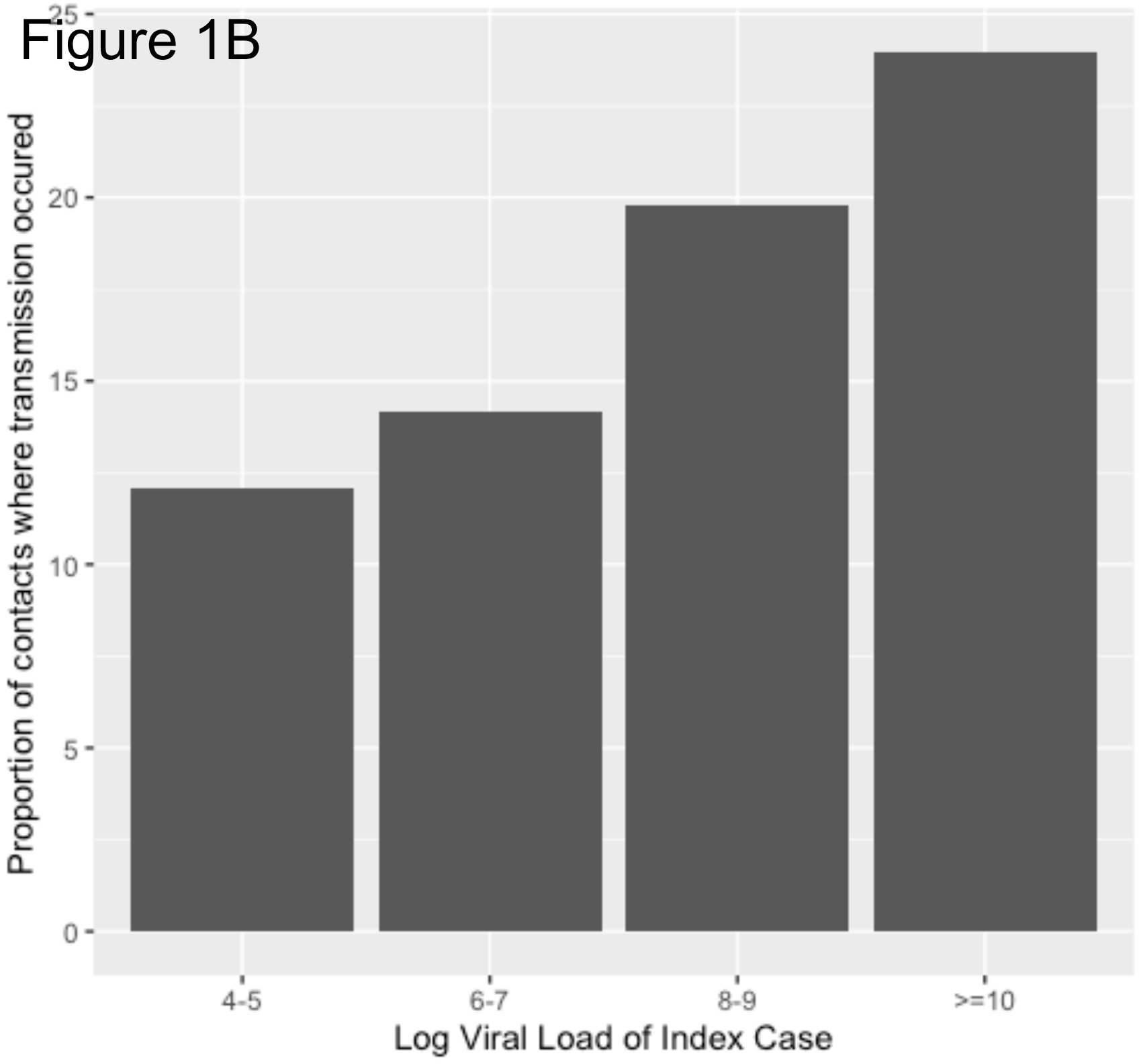

Proportion of contacts where transmission occured
25
20
15
10
5
0
4-5
6-7
8-9
>=10
Log Viral Load of Index Case

Figure 2A

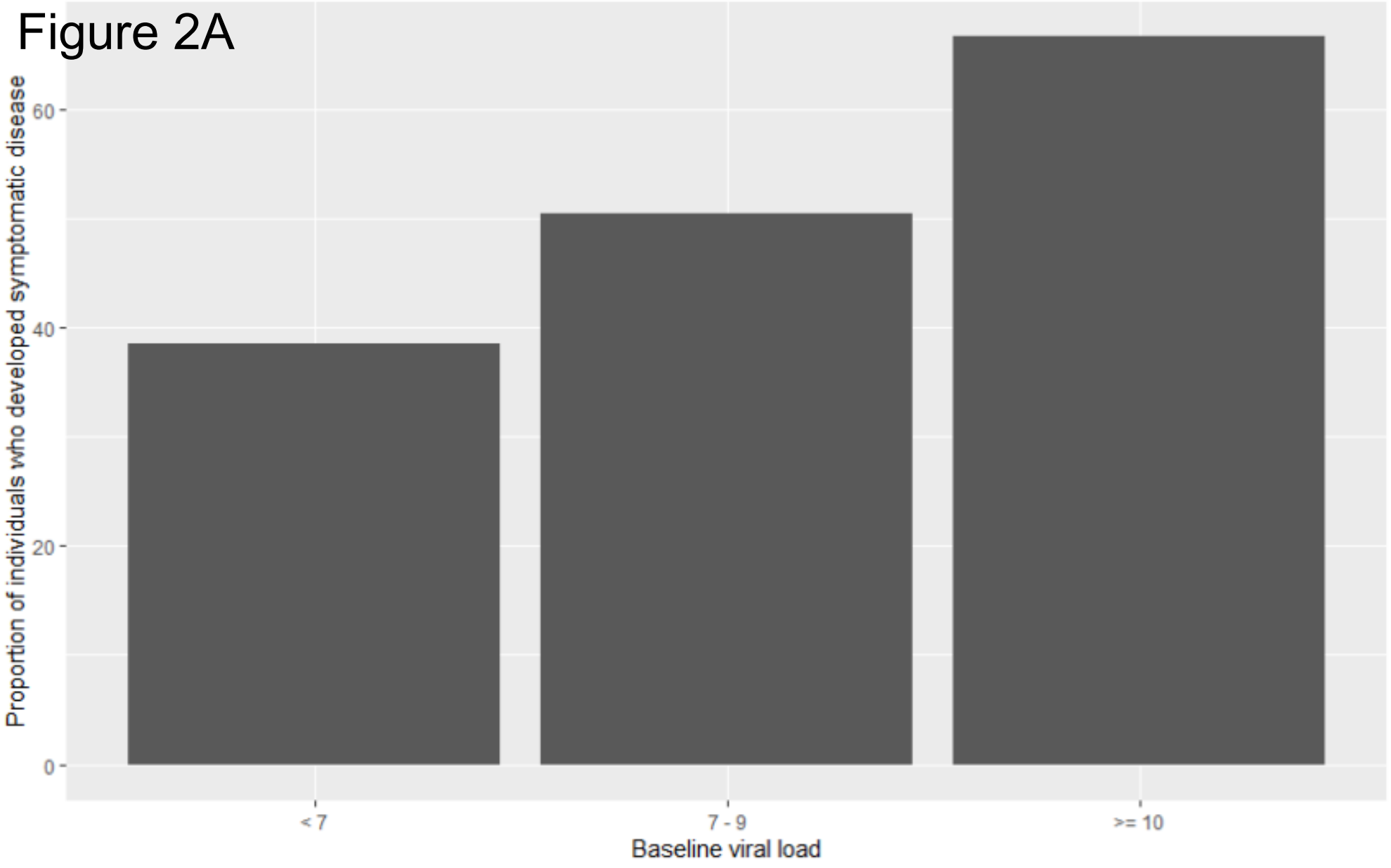
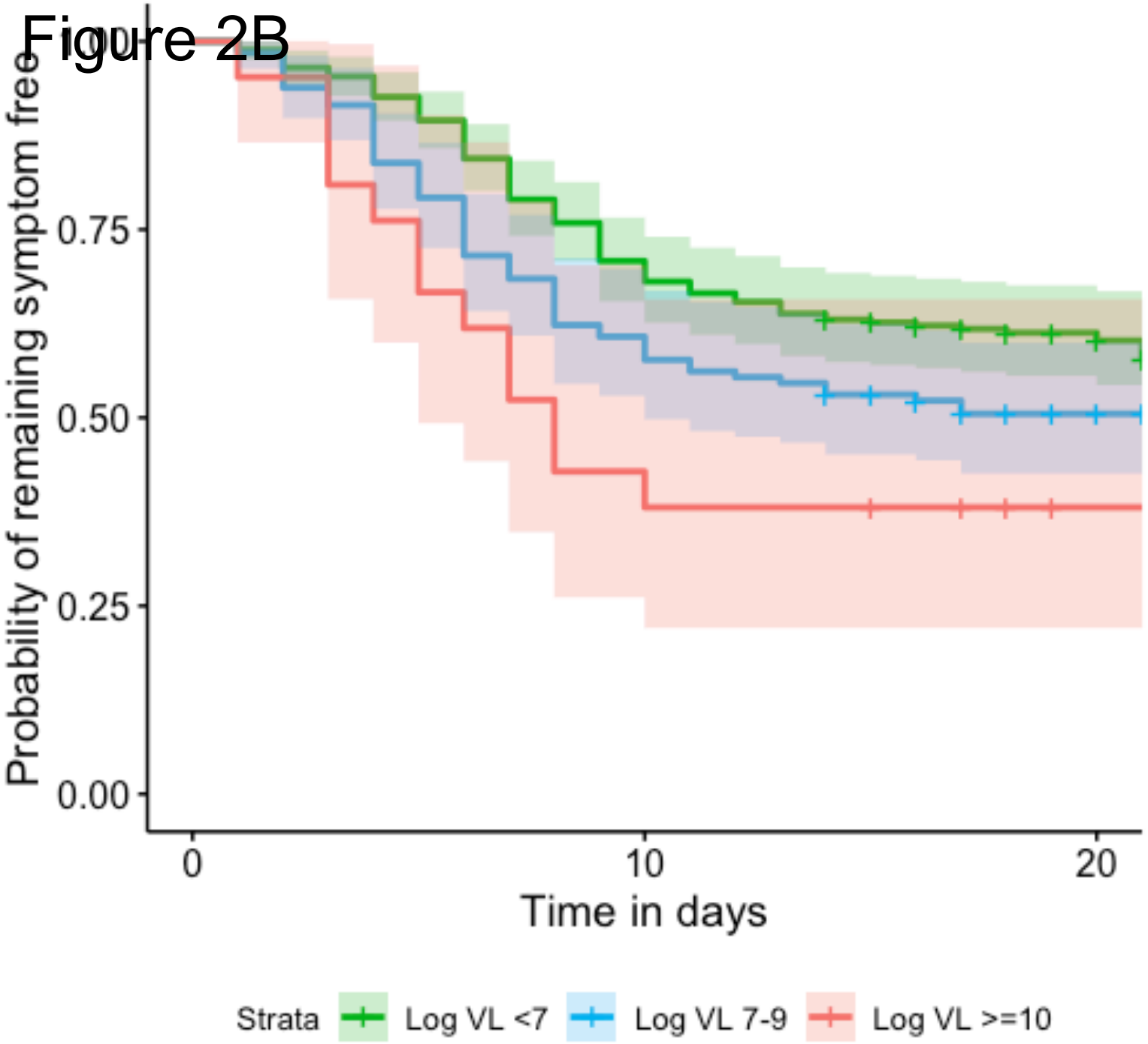
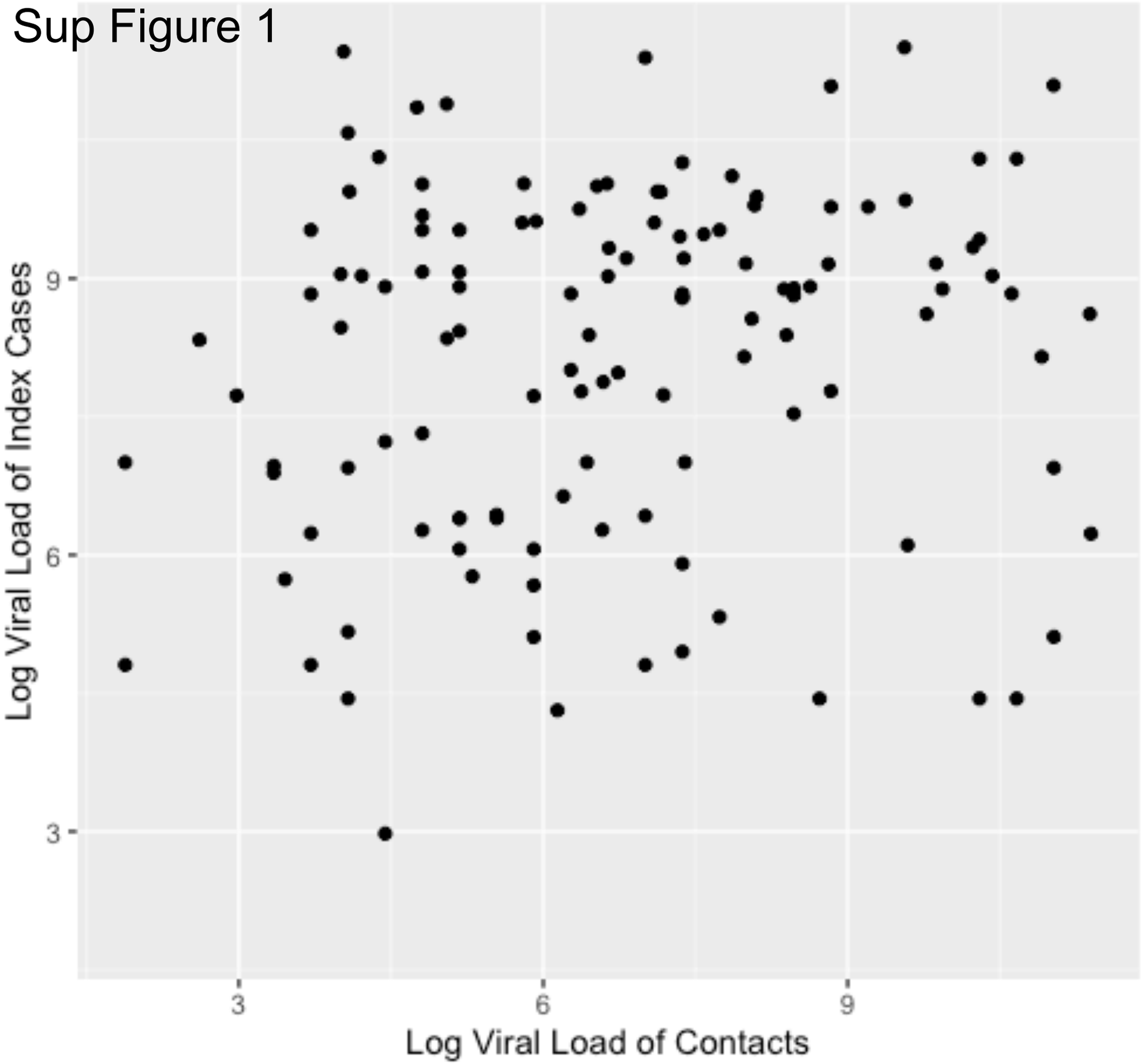

Proportion of individuals who developed symptomatic disease
60
40
20
0
< 7
7 - 9
>= 10
Baseline viral load

Figure 2B


Probability of remaining symptom free
1.00
0.75
0.50
0.25
0.00
0
10
20
Time in days
Strata
Log VL <7
Log VL 7-9
Log VL >=10

Sup Figure 1


Log Viral Load of Index Cases
9
6
3
3
6
9
Log Viral Load of Contacts