

Assessing asymptomatic, pre-symptomatic and symptomatic transmission risk of SARS-CoV-2

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Summary: Pre-symptomatic transmission of COVID-19 accounted for 38% of all infections occurred from exposure to symptomatic cases. Asymptomatic SARS-CoV-2 infections posed a lower risk to further transmission than symptomatic COVID-19 cases.

ABSTRACT

Background: The relative contributions of asymptomatic, pre-symptomatic and symptomatic transmission of SARS-CoV-2 have not been clearly measured although control measures may differ in response to the risk of spread posed by different types of cases.

Methods: We collected detailed information on transmission events and symptom status based on laboratory-confirmed patient data and contact tracing data from four provinces and one municipality in China. We estimated the variation in risk of transmission over time, and the severity of secondary infections, by symptomatic status of the infector.

Results: There were 393 symptomatic index cases with 3136 close contacts and 185 asymptomatic index cases with 1078 close contacts included into the study. The secondary attack rate among close contacts of symptomatic and asymptomatic index cases were 4.1% (128/3136) and 1.1% (12/1078), respectively, corresponding to a higher transmission risk from symptomatic cases than from asymptomatic cases (OR: 3.79, 95% CI: 2.06, 6.95). Approximately 25% (32/128) and 50% (6/12) of the infected close contacts were asymptomatic from symptomatic and asymptomatic index cases, respectively, while more than one third (38%) of the infections in the close contacts of symptomatic cases were attributable to exposure to the index cases before symptom onset. Infected contacts of asymptomatic index cases were more likely to be asymptomatic and less likely to be severe.

Conclusions: Asymptomatic and pre-symptomatic transmission play an important role in spreading infection, although asymptomatic cases pose a lower risk of transmission than symptomatic cases. Early case detection and effective test-and-trace measures are important to reduce transmission.

Keywords: SARS-CoV-2, COVID-19, asymptomatic, pre-symptomatic, symptomatic, transmission

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused 75 million human cases with coronavirus disease (COVID-19) worldwide since the virus was first identified in December 2019. People infected with SARS-CoV-2 show a broad spectrum of clinical manifestations, ranging from severe pneumonia through to mild acute upper respiratory symptoms, and some infections remain asymptomatic (1). With expansions in laboratory testing capacity, increasing numbers of asymptomatic infections and pre-symptomatic COVID-19 cases have been detected particularly from active monitoring of potentially exposed persons such as contacts of laboratory-confirmed cases or travellers returning from high-risk locations (2, 3). Some individuals can be diagnosed with laboratory confirmation in the absence of symptoms or prior to the appearance of symptoms. The patterns in virus shedding observed in asymptomatic and pre-symptomatic cases implied the potential for these individuals to be contagious (4, 5). In this study, we analyzed detailed contact tracing data to characterise the risk of transmission from symptomatic and asymptomatic individuals infected with SARS-CoV-2.

METHODS

Data sources

We retrospectively collected information on laboratory-confirmed symptomatic and asymptomatic SARS-CoV-2 infections (index cases) and their close contacts from four provinces and one municipality in China, Hubei, Jiangsu, Zhejiang, Guangdong and Chongqing during 5 January – 7 April, 2020. These data had been routinely collected since COVID-19 has been classified as a notifiable disease in China since early 2020. For each index case, we extracted information from the National Reporting System of Notifiable Infectious Diseases on age, sex, date of symptom onset (for symptomatic cases only), date of confirmation, number of close contacts, type of contact and severity status (asymptomatic, mild, moderate, severe, and critical). For all close contacts, we collected data on age, sex, start date and end date of contact with the index case, start date and end date of

quarantine, presence or absence of symptoms during quarantine, onset date of symptom (if any), date of specimen collection, laboratory test result for SARS-CoV-2, date of confirmation and severity status. Severity status was determined by the patient's attending doctors in the hospital following the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia published by the National Health Commission (1st- 7th versions) (Appendix).

Case definitions

Symptomatic COVID-19 cases referred to laboratory-confirmed SARS-CoV-2 infections who developed symptoms at confirmation, following the definitions provided in the Guidelines in Diagnosis and Treatment of COVID-19 published by the National Health Commission with seven updated versions since mid-January 2020 (6). Asymptomatic SARS-CoV-2 infections were patients who tested positive for SARS-CoV-2 without presenting any symptoms potentially related to COVID-19, such as fever, chill, dry cough, nasal congestion, loss of taste or smell, runny nose sore throat, headache, tiredness, muscle pain, joint pain, short of breath, difficulty breathing, conjunctivitis, nausea, vomit, diarrhoea, abdominal pain, etc., and without lung infections indicated by a chest X-ray examination, throughout the course of infection. Following the guidelines for contact tracing, close contacts of symptomatic cases were individuals who had exposed to a confirmed patient of SARS-CoV-2 infection without wearing proper personal protection equipments (including practising optimal hand hygiene or wearing gloves, and wearing surgical facemasks and gowns) and/or stayed with the case in close proximity (<1m) in a close/semi-close environment such as household, office, elevator, etc., which should have occurred within two days before the onset of the symptomatic case until when the symptomatic index case was isolated. Close contacts of asymptomatic SARS-CoV-2 infections were people who had a close contact (same definition as above) with the confirmed asymptomatic index case within two days before the asymptomatic case provided specimens to test for SARS-CoV-2 to the time when the index case was isolated (Appendix). The index case was a laboratory-confirmed infection with SARS-CoV-2 who was first identified in a cluster of cases.

Inclusion and exclusion criteria

In our analysis, we only included index cases (both symptomatic and asymptomatic) and their close contacts based on the following criteria.

Inclusion criteria

1. Symptomatic index cases were confirmed with PCR and reported the date of symptom onset and the date of confirmation.
2. Asymptomatic index cases were confirmed with PCR and reported with the date of confirmation.
3. A close contact had a solely possible source of infection being the index case identified.
4. An identified close contact received RT-PCR tests for SARS-CoV-2 with nasal swabs provided during quarantine
5. The mode and time of the contact between the index case and the close contact can be clearly identified.

Exclusion criteria

1. Close contacts were potentially exposed to multiple confirmed cases (either symptomatic or asymptomatic).
2. Close contacts had the last exposure to the index case 7 days earlier than the onset of symptomatic index/confirmation of asymptomatic index as the potential risk of transmission from the index to the close contact through the exposure was assumed to be extremely low.

Statistical analysis

We described and compared the characteristics of symptomatic and asymptomatic index cases of SARS-CoV-2 infection. Secondary infections identified from close contacts of these index cases and the secondary attack rates were examined separately by type of the index. Secondary infections were classified by place where the contact between the index and the secondary cases would have occurred to investigate the potential transmission risk by setting of social mixing. We also examined the number of infections identified among all the close contacts of symptomatic index cases, and estimated the cumulative proportion of infected contacts against the date of symptom onset of the index to illustrate the risk of infection of an symptomatic case over time. Factors possibly affecting the risk of infection among close contacts of the index cases were explored, including age, sex, type of contacts between the index and the contact, the index case being symptomatic or not, and the geographic locations of the cases identified.

The data on the time of contact, time of laboratory confirmation and the time of symptom onset allowed us to explore the proportion of secondary cases generated from the close contacts of the symptomatic index and to infer the possible risk of transmission over time considering the onset time of symptoms for symptomatic index cases. Information on transmission pairs with available onset dates was collated and used to infer the infectiousness profile of symptomatic SARS-CoV-2 infections following a similar method as previously published by He et al. (7). The observed serial interval distribution was used as a convolution between the infectiousness profile and the known incubation period distribution. A gamma distribution was fitted to estimate the time-varying risk of infection $\beta(t)$ allowing for an early occurrence of infectiousness being c days prior to symptom onset of the index (pre-symptomatic transmission). Parameters of this gamma distribution were estimated using the maximum likelihood. With the estimated infectiousness profile and the information on transmission pairs associated with symptomatic index cases, we further examined the temporal probability of infection and the cumulative probability of infection per day during the exposure window in relation to the symptom onset of the index case using the proportional hazards model. The probability of pre-

symptomatic transmission was therefore estimated as the cumulative probability of transmission from symptomatic index to their close contacts before index onset, as ascertained by exposure and symptom onset dates. Sensitivity analyses were conducted to explore the impact of assumptions about the distribution of hazards before, on and after onset applied in the model on the estimation of the infectiousness profile (Appendix).

We also examined the seriousness of infected close contacts of symptomatic and asymptomatic index cases by classifying these secondary cases into the following categories: asymptomatic, mild, normal, severe and fatal cases based on the presentation during the clinical course and the final outcome of the infection episode. Definitions for asymptomatic, mild, normal, severe and fatal cases are provided in Appendix, and severe secondary cases were defined as secondary cases with the clinical status being severe or critical. All statistical analyses were conducted in R version 3.6.3 (R Development Core Team, 2020).

RESULTS

In this study, we obtained data on 578 index cases of COVID-19 and 4214 close contacts of these index cases to examine for the occurrence of infections given their exposure to the index patient (Figure S1). In total, 393 symptomatic index cases with 3136 close contacts and 185 asymptomatic index with 1078 close contacts were included into the analysis. The median age of the symptomatic index cases was similar to that of asymptomatic index patients (43 years vs 41 years) while there were more child and slightly fewer adult cases (45 years and older) in the asymptomatic index group than the symptomatic index cases (Table S1).

The median age was 39 years and 37 years for the close contacts of symptomatic and asymptomatic index cases, respectively. A variety of types of contacts were reported including living in the same

household, sharing meals, having conversations, healthcare contacts and sharing transportation, etc. More than one third of the contacts reported a household exposure in both the symptomatic and asymptomatic index groups, and contacts of asymptomatic index cases more frequently reported an exposure to an index through conversation (25% vs 16 %) (Table S2).

Overall, there were 140 infections identified from the 4214 contacts of both symptomatic and asymptomatic index cases. The proportion of infection was higher among the contacts exposed to symptomatic index cases (128/3136 ,4.1%) compared with those exposed to asymptomatic index cases (12/1078 ,1.1%) (Table 1). Among the infections identified in the contacts, 75% (96/128) were symptomatic in the contacts who were exposed to a symptomatic index, in compared to 50% (6/12) identified in the contacts of asymptomatic index cases. The proportions of infection among contacts were generally similar across the age and sex groups and geographical locations by type of index.

Among the symptomatic secondary cases in the contacts, all the symptomatic contacts of asymptomatic index (6/6) were classified as normal without cases being severe or fatal while 12 out of 96 infected symptomatic contacts of symptomatic index were fatal or severe (Figure S2). In the regression model, we found that the risk of infection was substantially higher among contacts who were exposed to a symptomatic index case than those with exposure to an asymptomatic index (OR: 3.79, 95% CI: 2.06, 6.95) (Figure 1). Besides, it was shown that contact type being household or shared meal were also associated with a higher risk of infection to close contacts.

With the data of infections identified among the close contacts of symptomatic index cases, we found that no infections was identified among contacts with the latest date of exposure to the index being two days before the onset of the index or earlier. About 12% (15/128) of the infected contacts were exposed one day before the symptom onset of the index or earlier (Table S3). Around 76% of the

infected contacts had the last exposure to the index within 7 days after the index's onset or before the index's symptom onset while 97% reported the last exposure being within 14 days after onset of the symptomatic index.

Using the information on these 96 pairs of symptomatic index cases and their infected symptomatic contacts, we estimated the infectiousness profile (Figure S3). As our estimate allowed for an early occurrence of infectiousness before onset, it was inferred that infectiousness started to increase from 7 days before the index onset, while infectiousness peaked around the onset. Based on the estimated hazard of infection, the cumulative proportion of transmission by a certain day and the probability of infection at a certain day were shown in Figure 2. Approximately 38% (95% CI: 28%, 49%) of the infections occurred before symptom onset of the index, and the probability of transmission peaked at around onset of the index and dropped rapidly within 5-7 days after onset to a very low level.

Results from the sensitivity analyses indicated that the model assumptions would not substantially affect the estimates of the infectiousness profile, with the proportion of pre-symptomatic transmission ranging from 29.6% to 40.7% and probabilities of transmission all peaked at onset under these four various conditions (Table S4, Figures S4-S5).

DISCUSSION

In this study, we collated detailed information on laboratory-confirmed COVID-19 index cases and their close contacts. The characterized transmission pairs allowed us to compare and infer the risk of transmission from symptomatic and asymptomatic index cases to their contacts and to explore risk factors for the transmission and for the observed severity of the infected close contacts. In addition to demonstrating that asymptomatic transmission did occur as in previous studies (5, 8), with this large sample of contact/transmission pairs, we showed that symptomatic index cases posed a higher risk of

transmission to their close contacts than asymptomatic index cases after considering the difference in exposure settings. More importantly, our study illustrated that the clinical presentations of infected contacts varied by the type of index cases exposed, i.e., secondary cases were more likely to be symptomatic if being exposed to symptomatic index cases, or be asymptomatic if exposed to asymptomatic index.

With improved case detection and test-and-trace, more COVID-19 cases were identified asymptomatic at confirmation (2). The majority of these early detected cases often came from quarantine as close contacts of a confirmed case while only a small fraction remained free of symptoms throughout the course of infection as asymptomatic cases (9, 10). It has been challenging to accurately record and report the numbers of asymptomatic infections which often required comprehensive testing and follow-up on individuals involving multiple departments in case identification and management especially when limited capacity was available as COVID-19 cases surged (11). Considerable uncertainty remains over the role that asymptomatic cases play in transmission of SARS-CoV-2 (11). In our study, we collected transmission pairs identified through contact tracing and verified information on the cases being truly asymptomatic or not. We found that asymptomatic index cases with SARS-CoV-2 infection were contagious, but posed a lower risk to transmit infections compared to symptomatic counterparts (8, 12).

The secondary attack rates in close contacts exposed to symptomatic index cases (4.1%) or asymptomatic index cases (1.1%) estimated in our study were generally lower than the reported from other studies (13-15). The difference in the observed secondary attack rates might be due to the varied investigation settings across the studies, and some studies specifically reported outbreaks in places where closer and more frequent contacts might have occurred (13, 16) while similar estimates were reported in another study (17). In addition, intense public health measures had been implemented in China during the study period, including active case finding and isolation, effective contact tracing

and widely adopted social distancing measures. These might have greatly reduced the numbers of close contacts and contact frequency and durations exposed to an infected case, and therefore led to a relatively low secondary attack rate in the close contacts.

Symptomatic and asymptomatic COVID-19 cases differed in many ways. For instance, symptomatic cases might generate more virus-laden particles because of the presented symptoms than asymptomatic cases leading to a higher risk of transmission to their contacts (17). On the other hand, symptomatic and asymptomatic cases might behave differently, including symptom initiated self-isolation, delay in healthcare seeking and therefore detection and isolation in asymptomatic infections (10, 18). It is still uncertain whether SARS-CoV-2 viral shedding profiles vary in asymptomatic and symptomatic cases although viral shedding seemed to decrease more slowly among symptomatic cases (4).

Previous studies characterised the risk of pre-symptomatic transmission with viral shedding data (7, 19), similar to the unimodal trend of infectiousness illustrated in our study peaking at around symptom onset among symptomatic cases. Pre-symptomatic transmission accounted for 38% of all transmission events occurred from our study, which was likely to be the upper limit of contribution to the overall infections since further transmission might have been interrupted by isolation of confirmed cases depending on the efficiency in case finding. Nonetheless, within our data, less than 1% of the close contacts were exposed to their index cases 5 days or later after the index onset, and the onset-to-admission delay was reported to be 8-14 days in China (4), indicating that our estimate suffered little from such interruption.

Our study also suggested that close contacts occurred in households or through shared dining were associated with a higher risk of transmission from the index to their close contacts than contacts

happened in other settings. The increased risk of infection in these occasions might be due to longer durations of exposure, social interactions in a closer distance, and perhaps not being able to wear facemasks properly (20). Studies on superspreading of COVID-19 indicated that a small proportion of cases were responsible for the majority of the transmissions occurred, and clusters of cases were often identified in places where unprotected contacts (without facemask wearing) happened for a longer duration (21).

Our study has several limitations. First, we constructed transmission pairs based on the relationship between the identified index cases and their close contacts. However, we could not rule out the possibility that an index case might have been misclassified as a primary case if the case only presented symptoms earlier but was infected later by the true primary case. Second, we did not collect data on virus testing, which was not ideal in exploring the risk of transmission from asymptomatic and symptomatic index cases although our findings were largely consistent with the viral shedding patterns described elsewhere (4, 7). Lastly, we could not estimate the temporal risk of transmission from asymptomatic index cases due to the lack of information on the time of infection of asymptomatic index and the relatively small number of infected close contacts exposed to asymptomatic cases.

Our study illustrated that the risk of transmission varied according to the symptom profile of COVID-19 cases. Asymptomatic cases transmitted infection to their close contacts at a lower risk than cases presenting symptoms. Pre-symptomatic transmissions accounted for more than one third of the infections occurred from exposure to symptomatic cases. Risk of transmission was relatively higher within households or through shared dining than other social settings. Active case finding with increased testing capacity could help to reduce transmission from symptomatic and asymptomatic COVID-19 cases. Social distancing measures and facemask wearing might not be sufficient to prevent infection from spreading in settings where these measures could not be maintained.

NOTES

AUTHOR CONTRIBUTIONS

All authors meet the ICMJE criteria for authorship. The study was conceived by ZC and ZL. Data collection and cleaning were conducted by FL, MR, CZ, YL, ZP, YQ, JY, MG, XY, HZ, ZL, SZ, LR, QC and LW. Data analyses were done by FL, YL and TKT. PW wrote the first draft of the manuscript. All authors provided critical review and revision of the text and approved the final version.

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COMPETING INTERESTS STATEMENT

BJC consults for Roche and Sanofi Pasteur. All other authors report no other potential conflicts of interest.

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FIGURE LEGENDS

Figure 1. Risk factors potentially associated with the transmission risk of SARS-CoV-2 shown with the estimated odds ratio and 95% confidence intervals from a multivariable regression analysis adjusting for age groups, sex and regions.

Figure 2. Temporal risk of transmission from symptomatic index to their close contacts in relation to the time of index onset. Panel (A): Cumulative proportions of infection in relation to the clinical presentation of symptomatic index cases; Panel (B): Probability of infection in exposed close contacts in relation to the clinical presentation of symptomatic index cases. The red dots refer to the point estimate, and the error bars correspond to the estimated 95% confidence intervals.

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Table 1. Characteristics of infected close contacts of symptomatic and symptomatic index of SARS-CoV-2 identified in Hubei, Guangdong, Jiangsu, Zhejiang and Chongqing in China.

	All contacts (N=4214)	p-value ‡	Contacts of symptomatic index (N=3136)	p-value	Contacts of asymptomatic index (N=1078)	p-value	p-value (symptomatic vs asymptomatic)
Infected close contacts	140/4214 (3.3%)		128/3136 (4.1%)		12/1078 (1.1%)		<0.01
Symptomatic	102/14 (72.9%)		96/128 (75%)		6/12 (50%)		0.09
Age, years							
0-14	13/476 (2.7%)		13/348 (3.7%)		0/128 (0%)		0.02

15-44	59/205 9 (2.9%)		56/1510 (3.7%)		4/549 (0.7%)		<0.01
45-64	49/129 3 (3.8%)		42/970 (4.3%)		7/323 (2.2%)		0.09
65+	19/415 (4.6%)	0.21	18/331 (5.4%)	0.49	1/84 (1.2%)	0.15	0.14
Sex							
Male	60/227 4 (2.6%)		58/1682 (3.4%)		2/592 (0.3%)		<0.01
Female	80/194 0 (4.1%)	0.01	70/1454 (4.8%)	0.06	10/486 (2.1%)	0.01	0.01
Symptoms #							
Present	102/169 (60.4%)		97/152 (63.8%)		5/17 (29.4%)		0.01
Absent	38/404 5 (0.9%)	<0.01	31/2984 (1.0%)	<0.01	7/1061 (0.7%)	<0.01	0.35
Region							
Hubei	32/989 (3.2%)		30/585 (5.1%)		2/404 (0.5%)		<0.01
	34/127		32/946 (3.4%)		2/327 (0.6%)		<0.01

Guangdong	3 (2.7%)							
Jiangsu	36/973 (3.7%)	33/861 (3.8%)		3/112 (2.7%)			0.79	
Zhejiang	16/304 (5.3%)	15/189 (7.9%)		1/115 (0.9%)			0.01	
Chongqing	22/675 (3.3%)	0.23 18/555 (3.2%)	0.04	4/120 (3.3%)		0.03	1	
Type of contact								
Household	104/1516 (6.9%)	96/1105 (8.7%)		8/411 (1.9%)			<0.01	
Shared meal	14/444 (3.2%)	11/395 (2.8%)		3/49 (6.1%)			0.19	
Medical reasons	1/209 (0.5%)	1/192 (0.5%)		0/17 (0%)			1	
Shared transportation	1/397 (0.3%)	1/309 (0.3%)		0/88 (0%)			1	
Conversation	7/769 (0.9%)	7/504 (1.4%)		0/265 (0%)			0.1	
No direct contact*	2/283 (0.7%)	2/240 (0.8%)		0/43 (0%)			1	
Multiple contacts	4/134 (3%)	4/96 (4.2%)		0/38 (0%)			0.58	
Others**	7/462	6/295 (2%)		1/167 (0.6%)		0.04	0.43	

(1.5%) <0.0

1

<0.01

*No direct contact refers to close contacts exposed to the environment contaminated by cases infected with SARS-CoV-2 whereas without direct contact with the infected case (Appendix).

**Others refer to other individuals assessed by onsite investigators meeting criteria for close contact (e.g., individuals who have had close contact in an office, factory, workshop, elevator, canteen, etc.).

‡The p values indicate the statistical significance for comparison of the proportions of infected close contacts between groups under each variable listed in the table.

#Symptoms include fever, chill, dry cough, nasal congestion, loss of taste or smell, runny nose sore throat, headache, tiredness, muscle pain, joint pain, short of breath, difficulty breathing, conjunctivitis, nausea, vomit, diarrhoea, abdominal pain, etc.

Figure 1

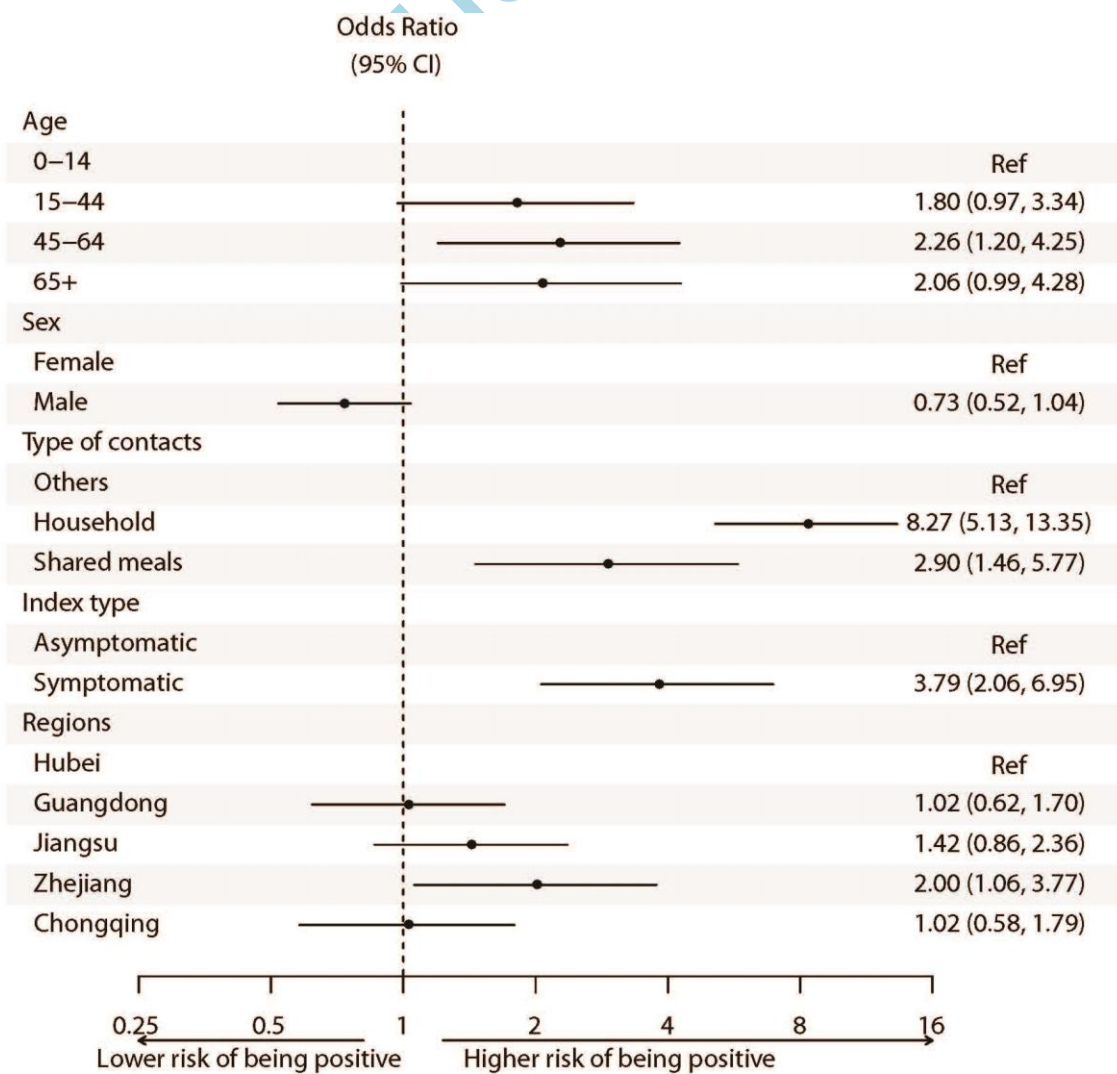


Figure 2

