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**Intra-familial transmission pattern of COVID-19 infection among the rural residents in
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Summary:

We are yet to completely understand the transmission dynamics of COVID-19 which is a highly infectious disease and research exploring the same is lacking. Hence, a community-based cross-sectional study was conducted aiming to assess the intra-familial transmission pattern among the rural residents of Ahmedabad, Gujarat in relation to possible determinants with special focus on viral load as an important determinant. A cross-sectional study was done where 195 families were visited. Families having at least one infected case, were interviewed. Information about their socio-demographic profile and secondary transmission of case/s were recorded. Out of 195, 114 families confirmed to having at least one infected case within the family. About 38.6% (44/114) of the index cases were asymptomatic, which was much higher among low viral load index cases. Index cases with high, moderate and low viral load had transmitted the infection with an average of 3.3, 1.5, 0.4 secondary cases per index case respectively. About one third of COVID-19 infected cases was asymptomatic and was capable of spreading the disease within families. Secondly, index cases with higher viral load had higher transmission potential to generate more secondary cases compared to low viral load.

Introduction:

The pandemic, caused by SARS-CoV-2, has afflicted the world resulting in unmatched destructive outcomes. The world has not faced such a mammoth situation in almost a century. This worldwide outbreak triggered a large number of fatalities, morbidities, and has cost billions of dollars (1). Compared to other diseases and their respective burdens, COVID-19 is likely to cause greater human suffering than any other contagious diseases in the whole world. The COVID-19 pandemic is caused by a newly discovered corona virus, SARS-CoV-2, which is the third epidemic to come up after SARS in 2003 and MERS in 2012 (2). India

experienced its first confirmed case on January, 2020 when a medical student returned from Wuhan, China (3). Since then, India has witnessed its epidemic curve with an increasing number of daily cases, which reached its plateau on September 18th, 2020 with close to 98,000 daily cases and then declining with 18,222 cases as on 9th January, 2021(4).

Earlier study conducted by ICMR-NIOH, had conclusively evidenced that viral load is an important determinant for transmission of COVID-19 infection during an epidemic. Viral load was assessed using cycle threshold (Ct) value of real time RT-PCR test of infected cases. The study observed that infected cases were mostly clustered around the houses of infected cases with high viral load. The study assessed that a case with high viral load had an average of 6.25 secondary cases whereas cases with low viral load had the same of 0.8 case (5). This made us hypothesize that if an index case with high viral load is quarantined within a family, it will transmit the infection to more number of secondary cases as compared to the same with low viral load if necessary precautionary measures are not practiced by the family members all throughout the course of the disease including while sleeping at night.

With above understanding and background, this study was planned to assess the intra-familial transmission pattern among the rural residents of Ahmedabad, Gujarat in relation to viral load of the index/first case within the family.

Material and Methods:

It was a community based cross-sectional study to assess the intra-familial transmission pattern and the associated risk factors for transmission with special focus on viral load as an important determinant within the families of residents of rural Ahmedabad during the COVID-19 epidemic. Within the rural Ahmedabad district, there are 9 sub districts, out of which two were chosen purposively. The study population was chosen conveniently from the villages of the chosen sub districts. A total of 195 families were visited from these villages,

while visiting the study area. Families having at least one infected case within past three month from the date of visit were recruited for this study. The first infected case within the family was considered as index case and subsequent cases occurring within the longest incubation period (ranging from 2-14 days) were considered as secondary cases. The study was conducted through house to house visits by the trained field workers using a pretested questionnaire. The questionnaire included relevant information such as socio-demographic profile, secondary transmission of case/s etc. Necessary consent was obtained from all the participants before collection of information. Socio-economic status was assessed using per capita income (PCI) as a composite indicator. Socio-economic status was categorized into poor ($PCI \leq 1000$), lower middle class ($PCI = 1001-5000$), upper middle class ($PCI = 5001-10,000$) and upper class ($PCI > 10,000$). The study was conducted in May & June, 2021. Viral load of index cases was assessed using cycle threshold (Ct) value of real time RT-PCR test report as a proxy marker as was done in a previous study conducted by Indian Council of Medical Research-National Institute of Occupational Health (ICMR-NIOH)(6). Viral load was categorized by Ct values of 31 to 38 as low, 24 to <31 as moderate and 17 to <24 as high viral load. The real time RT-PCR tests were done at nearby local laboratories and Ct values were obtained from their test reports. Laboratory to laboratory variation was minimised by the internal and external quality assurance programme of laboratories under the guidance & coordination of state referral laboratory as well as national referral laboratory (ICMR-National Institute of Virology). It may be noted that both naso-pharyngeal and oro-pharyngeal samples were collected from each suspected infected individual at the early phase of symptomatic or asymptomatic persons having contact history with a confirmed positive case to assess initial viral load. An asymptomatic laboratory-confirmed case is a person infected with SARS-CoV-2 virus, who does not develop symptoms (as defined by WHO) has been considered in this study. “Asymptomatic transmission refers to transmission of the virus

from a person, who does not develop symptoms” (7) has also been considered for this study. Categorization of infectivity of index cases was done based on viral load indicated by Ct value. Details of index as well as secondary cases were noted using pretested questionnaire. Data was transported to ICMR-NIOH on the same day of collection and edited on the same day. Entry and analysis of edited data was done by using STATA, 15.0 software. Ethical clearance was obtained from the Institute Ethics Committee of ICMR-NIOH before initiating the study.

Results:

A total of 195 families were visited. Of them, 114 families confirmed of having at least one case within the family within past 3-month from the date of visit, who suffered from infection. A total of 157 infected cases (index as well as secondary cases) were available, who were eligible for this study. Demography and socio-economic profile of the index cases are presented in table no-1.

It is evident from the table that males outnumbered the females and most cases were below the age of 60 years. Socioeconomically, most participants were upper middle class (52.6%) and literacy-wise most participants were either graduate or above. Figure-1 present the distribution of cases based on presence or absence of symptoms and its relationship with viral load.

In this study, 44 out of the total 114 (38.6%) index cases were asymptomatic, out of which, index cases with low viral load were the highest (48.3%; 29 out of 60) followed by moderate (29.2%; 7 out of 24), followed by cases with high viral load (26.7%; 8 out of 30).

Table-2 depict in details the distribution of index cases with viral load and their corresponding secondary cases. It is evident that 30 index cases with high viral load had transmitted 100 secondary cases with an average of 3.3 secondary cases per index case.

Similarly, 24 index cases with moderate viral load had transmitted infection to 36 secondary cases with an average of 1.5 secondary cases per index case. Finally, 60 index cases with low viral load transmitted to 21 secondary cases only with an average of 0.4 case per index case. Alternatively, it may be said that intra-familial transmissibility was 8.3 and 3.8 times higher for cases with high and moderate viral load compared to the same of low viral load as reference transmission value. Clubbing all index cases of different viral load together, each case generates 1.4 secondary cases (157 cases out of 114). Special attention may be given to one of the index cases of high viral load, which has generated 14 secondary cases as seen in table-2. The study attempted to analyse the data on the relationship between transmission pattern (generation of secondary cases from index cases) and socio-economic status, family size, protective measures taken etc. But it showed no statistically significant difference between the transmission pattern and the above-said factors. Unfortunately, consistent individual preventive behaviour was lacking in the study community, hence it could not be analysed.

Discussion:

Disease transmission of COVID-19 outbreak, it was found that they are not uniformly transmitted, some have higher potential to transmit, some have lower and some in-between. Earlier study conducted by ICMR-NIOH revealed that index cases having high viral load spread infection almost 8 times higher compared to the same of low load (5). The said study observed that high number of secondary cases was clustered around the location of index cases with high viral load indicated by Ct value as discussed already. This study wanted to explore whether the same holds true for intra-familial transmission of cases. The study has explored two interesting observations as depicted below:

First, it was observed that overall, about 38.6% (n=44) of the total index cases were asymptomatic. Asymptomatic index cases with low viral load were found to be the highest (48.3%; n=29), followed by 29.2%(n=7), followed by 26.7%(n=8) among index cases with moderate and high viral load respectively. This has tremendous significance for community transmission of COVID-19 cases during an epidemic situation particularly in an Indian rural community where awareness level is inadequate, hygienic practices including hand hygiene, physical distancing, usage of mask etc. are poor. Moreover, during sleeping at night, people usually avoid using face mask, maintaining required distance facilitating transmission particularly in overcrowding situation. It may be noted that asymptomatic and pre-symptomatic cases with higher viral load are understood to be spreading infection unknowingly while breathing, talking, singing, shouting etc. during his/her infectious period similar to symptomatic cases although they look apparently healthy to others. It appears like asymptomatic cases may spread more number of secondary cases compared to symptomatic cases during their pre-symptomatic period, particularly cases with high viral load, probably because of their ignorance of their status. Cases of this kind will definitely pose a greater threat compared to symptomatic cases for intra-familial transmission as well as community transmission while moving out of the family. Extensive community as well as family level awareness is needed to make them aware with practicing above said safer practices such as hand hygiene, physical distancing & use of face mask. Probably the period of viral shedding is longer among cases with high viral load as was observed in a study from Nanchang, China, which has recorded the finding which suggests that high viral load cases are likely to have severe COVID-19 infection and a prolonged period of viral-shedding whereas, it was found that viral clearance is early in mild cases (8). The same study also observed the fact that compared to mild cases, the mean viral load was almost 60 times higher in severe cases. Therefore, they too have suggested viral load to be a helpful marker for estimating severity of

the disease and its prognosis. However, further in-depth studies are required to have consistency of this observation.

Intra-familial transmission in this study revealed that index cases with higher (high & moderate) viral load generated significantly higher secondary cases compared to index cases of low viral load apart from other factors such as socio-economic status, family size, lack of hygienic practices, population density and population mobility etc. However, the present study did not find any association between transmission of secondary cases and socio-economic status and family size (overcrowding) in the studied families probably due to low number of studied subjects or it could be due to the fact that cases with higher viral load are powerful transmitter undermining other factors such as socio-economic status and/or family size etc. This is because it was observed (outside study area) that in many high as well as low socio-economic families with/without overcrowding, intra-familial transmission of secondary cases occurred when viral load of index case was high but not with the same of low viral load with same degree of standard protective measures (personal observations from family friends having infected cases in their families). Transmissibility of cases with low viral load is quite low as observed in this study. Since the home quarantine for cases with higher viral load is expected to facilitate higher intra-familial transmission of cases as observed in this study, therefore, home quarantine is not suggested for them. On the other hand, same with low viral load may be quarantined at home with standard physical distancing, hand hygiene and wearing face mask. Similarly, cases with higher load need to be quarantined away from families (institutional quarantine). These recommendations are consistent with the previous study conducted in Gujarat, India, which has successfully demonstrated that viral load based segregation with required contact tracing showed a significant decline of cases up to 50% within 3 weeks following the day of implementation in the intervention area (Ahmedabad district) compared to non-intervention area of the state (9). Presently, COVID-19 epidemic is

largely concentrated in cities & urban areas that are gradually approaching towards semi-urban/rural areas through population movement. More number of rural population are expected to become infected if not vaccinated in coming days since 60-70% of developing country's population reside in villages. Vaccination coverage for entire country with its 1.4 billion population will take long time, particularly in rural India. Considering the above, primary health care physicians must prepare themselves on Ct value-based segregation of COVID-19 infected cases with contact tracing of cases with high & moderate viral load of previous five days to reduce transmission of cases in the community, at least till all remote & rural population is protected with vaccination.

A systemic review of all global studies on secondary attack rate (SAR) of COVID-19 in non-household contacts found that SAR varies widely across countries with lowest reported rate as 4.6% and highest as 49.56%. It also reported that highest risk of SAR was seen in the non-household (family, friends) contact (2.2-22.31%) (10). Jing et al., has also confirmed that COVID-19 is more transmissible in household than SARS and MERS coronavirus (11). Review suggested greater vulnerability of spouse and elderly population for secondary transmission than other household members (10). Other studies have also found elderly population to be more vulnerable (11-12). Although a study from China found that children are at the same risk of infection like others (13) but this study did not observe such risk among children.

It was observed in a study that cases with initial high viral load are independently associated with worse survival (14). Similar kind of study from China has also reported that severity of COVID-19 was related to high viral load, they reported Ct value was negatively correlated with the probability of progression to severe type of disease in all patients representing mild to moderate severity at admission (15). Although the present study didn't observe the same,

as all cases recovered successfully except one case with high viral load, which died during immune dysregulation phase.

In many infectious disease outbreaks, it was seen that a small group of infected cases, termed as “the super spreaders” were seen contributing to majority of the disease transmission. Such events were also recorded in numerous other infectious diseases like measles, HIV, SARs, tuberculosis, typhoid, Ebola hemorrhagic fever (16-22). Accordingly, this study also observed an interesting case of an intra-familial transmission in which an index case with high viral load transmitted the infection to 14 other persons (secondary cases). He had travelled to another city and got infected. Within two days after he came back, he went to a family get together where 11 other family members got the infection. Not only this, 3 other colleagues were infected after his visit to the office. This is a vivid case of a super spreader. He had high viral load and was an asymptomatic case and as he was unaware of his status, he didn't take the recommended precautions seriously. Coupled with above, probably he was a prolonged shedder of viruses as mentioned in a study (8). Further in-depth study is required to explore the details of super-spreaders such as viral duration of shedding, presence/absence of symptoms, population density, mobility, lack of awareness etc.

To our knowledge, this is the first intra-familial transmission study conducted in South Asia to understand the transmission dynamics based on their viral load. However, we had some limitations like relatively low number of study subjects, problems associated with self-reported behavior of study subjects, lack of statement of comparison group, information about individual susceptibility, lack of information related to some relevant behavior such as room sharing, consistent use of face mask, physical distancing and frequent hand sanitization, lack of information on hospitalization, possible contamination from disposed items near residential area are some of the limitations. Although the present study has documented an

important aspect of intra-familial transmission, however, it needs to be further validated in a bigger population to assess its generalizability.

The present study has evidenced two useful facts of COVID-19 transmission during an epidemic situation. About 38.6% of the study participants were asymptomatic and capable of transmitting the disease knowingly or unknowingly. Appropriate need based intervention measures are needed for them. Secondly, index cases with higher viral load cause higher intra-familial transmission. Hence, if we want to save the population from getting infected and curb the transmission, viral load based segregation may be done as discussed above, particularly in the absence of a suitable vaccine or before it reaches to the remote locations. Extensive community & family awareness as well as adoption of hygienic practices, must be practiced on regular basis, which are essential steps for containing an epidemic in addition to above-said measures along with safe disposal of contaminated items. The local health authorities should focus on this issue and must consider the above recommendations.

Lastly, effective vaccination programme is perhaps the most efficient public health tool to prevent an epidemic. In this study, community vaccination was just initiated at the time of this study. Hence, the effect of vaccination in preventing or reducing epidemic was not expected for already occurred and transmitted cases. India used both Covaxin (about 20%) and Covishield (about 80%) for immunizing its citizens. Other countries, such as USA used Pfizer and Moderna vaccines. Most of these vaccines have a protective efficacy between 70–80%, which depends mainly on circulating viral strains in the local community and proper cold chain maintenance including vaccine storage and transporting system.

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Conflict of interest: None

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Figure Legend:

Figure-1: Infected index cases with/without symptoms and its relationship with viral load (n=114)

Tables:

Table-1: Socio-demographic profile of the infected index cases (n=114)

Socio-demographic characteristics	Number (%)
Gender	
Male	72(63.2)
Female	42(36.8)
Age	
<60	96(84.2)
>60	18(15.8)
Socio-economic status	
Poor	10(8.8)
Lower middle	44(38.6)
Upper middle	60(52.6)
Upper	0(0)
Highest education of any family member	
Illiterate	0(0)
Primary education	2(1.8)
Secondary education	34(29.8)
Graduation and above	78(68.4)

Table-2: Distribution of index cases with viral load and their transmitted secondary cases

	Sl. No. Index case	Frequency of Index case having similar number of secondary cases	Total no. of secondary cases generated by each index case of previous row	Total no. of secondary cases
High load	1	7	1	7
	2	10	2	20
	3	4	3	12
	4	5	4	20
	5	1	6	6
	6	1	9	9
	7	1	12	12
	8	1	14	14
Moderate load	1	14	1	14
	2	8	2	16
	3	2	3	6
Low load	1	39	0	0
	2	21	1	21
Total		114		157

Figure-1: Infected index cases with/without symptoms and its relationship with viral load (n=114)