Chapter

Control of an Epidemic of SARS-CoV-2 by Assessing Transmissibility of Its Infected Cases in Absence of a Suitable Vaccine

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Abstract

SARS-CoV-2 or Covid 19 and it's pandemicity has been wreaking havoc in many countries worldwide. It is important to counter and contain the spread of Covid-19 using some effective infection control policies as we await an effective protection such as vaccine. Ahmedabad Model of Covid-19 Control could be used as an established epidemic management protocol for COVID 19 infection. It relies on the Cycle Threshold (Ct) Value, which was used as a proxy marker for assessing initial viral load. It was evident that cases with higher viral load spread the disease at much higher rate as compared to that of low viral load apart from population mobility and/or population density. Therefore, Ct value based segregation of infected cases with higher viral load along with contact tracing of them of previous 5 days is an effective epidemic control policy. It needs to be remembered that a section of infected cases is asymptomatic and capable of spreading infection in the community unknowingly. Hence, infection control practices must be accompanied with standard precautionary measures such as physical distancing, hand hygiene and wearing face mask. Community awareness is an integral part of it. Newer biotechnology based researches may be encouraged based on felt needs.

Keywords: SARS-CoV-2, epidemic, cycle threshold value, RT-PCR, transmissibility

1. Introduction

SARS-CoV-2 or COVID-19 is a newly discovered coronavirus representing the third coronavirus associated epidemic to emerge from a species leap i.e. from the wild animals to the humans, after severe acute respiratory syndrome (SARS) in 2003, and the Middle East Respiratory Syndrome (MERS) in 2012 [1]. COVID-19 transmission dynamics is yet to be understood thoroughly. Basic Reproduction Rate (R_0) is a term which is often used in an epidemic. It is the average number of secondary cases of an infectious disease that one case would generate in a completely susceptible population within its longest incubation period [2]. If $R_0 > 1$, then the number of infected cases is likely to rise, while if $R_0 < 1$ then the transmission will probably die out. The basic reproduction number is an important measurement

in infectious disease epidemiology, indicating the risk of an infectious agent with respect to epidemic spread. Estimated basic reproductive number of COVID-19, declared by the WHO (dated January 23, 2020) ranges within 1.4–2.5 [3].

A recent review by Liu et al. found the average R_0 of COVID 19 infection to be 3.28 and median to be 2.79, which exceed the WHO estimates [4]. It was observed in SARS that a few of the infected people in the community spread most of the infection, whereas most people, although infected, spread it to only a handful [5–12]. In addition to R_0, scientists use a value called dispersion factor (K), a number that indicates the likelihood of a certain disease to spread in clusters [13]. Lower the K value, more is the transmission that occurs from a small number of people. In 2005, an article in Nature estimated that SARS had a K value of 0.16 [13]. In a recent publication, K value for COVID-19 was estimated to be as low as 0.1 [14] suggesting that probably about 10% of the total number of infected cases will be spreading to about 80% of the cases.

Apart from Basic Reproduction Rate, certain other terminologies are just as important to understand the transmission pattern of infected cases in a community or in a defined geographical area. The term epidemic is used when there is occurrence of large number of infected cases in a community or in a defined geographic area and in a particular period, clearly in excess than the expected number of cases during the same time of previous years. When the occurrence of cases is less than that of the expected number of cases compared to previous years, it is called endemic. Epidemic may be common source epidemic (all cases occurring simultaneously from a single source such as food poisoning following consumption of a meal at a marriage party) or propagated epidemic (when few cases occur from a source and then they further infect some other people, who in turn spread to another group). Certain factors are associated with transmission of infection such as virulence of organism, organisms' density in infectious material, lack of health seeking behaviour, population density, population movement, lack of awareness, lack of hygienic practices, etc. The infectiousness of an infectious disease is measured by Secondary Attack Rate (SAR) - defined as the occurrence of new cases among the susceptible population from the primary case within the longest incubation period of that disease. Usually it is expressed in percentage. Secondary Attack Rate depends on population density, population mobility, virulence of organism, organism density, behaviour of the individuals concerned, etc. in absence of any intervention such as vaccination or medication.

A review work was carried out by a group of researchers that raised several questions. COVID-19 via person-to-person contact had had spread like a wildfire, affecting almost every country in the world. In the past 100 years, the world never experienced a pandemic as cataclysmic as COVID-19. It is easily understood that both previous outbreaks of other members of the coronavirus family (severe acute respiratory syndrome (SARS-CoV) and middle east respiratory syndrome (MERS-CoV)) did not produce even 2% of the global harm which has already been inflicted by COVID-19. There are also four other CoVs capable of infecting humans (HCoVs), which circulate continuously in the human population, but their phenotypes are generally mild, and these HCoVs have received little attention. These dramatic differences between infection with HCoVs, SARS-CoV, MERS-CoV, and SARS-CoV-2 raise many questions, such as: How quick transmission occurs in COVID-19? Does viral structure play any role in it? Any specific human (host) factors are involved? Any environmental factors involved? A review work was done by a group of researchers with the aim of having possible logical answers to above questions [15].

Data collected in above mentioned review clearly indicated that SARS-CoV-2 uses multiple ways for efficient transmission. The virion structure is optimised to survive various environmental conditions, allowing this virus to use both respiratory and faecal-oral transmission modes. Its S protein has an amended structure

for efficient interaction with the ACE2 receptor and is optimised for furin cleavage. Moreover, S protein could be primed with activation by TMPRSS2, furin, and multiple non-furin proteases (e.g., plasmin). In addition to ACE2, SARS-CoV-2 can interact with other cellular peptidase receptors, such as ANPEP and DPP4, and also can utilise non-peptidase receptors, such as DC-SIGN1, CLEC4G, and CLEC4M. SARS-CoV-2 utilises multiple ways for cellular entry (both non-endosomal and endosomal) and potentially uses various means of epigenetic control to inhibit the initiation of the host innate immune response. During pandemic period continuous genetic rearrangements occurs within the virus cell genetic structure, which enable the virus particles for immunological escape. SARS-CoV-2 is associated with intricate interplay involving various host genetic factors and pathways. Cytokine storm is the result of above interactions, which promotes cellular death programme of various cells, such as pyroptosis, apoptosis, and necrosis, which might contribute to the COVID-19 pathogenesis. This remarkably broad spectrum of means for the efficient SARS-CoV-2 transmission indicates that it is very unlikely that COVID-19 can be cured by targeting just one segment of this complex mosaic [15].

2. Recent experience from India

India had had witnessed a tremendous rise in the daily number of COVID-19 infected cases during its epidemic period. It started from January 2020 with single detected case in Kerala that reached its plateau in mid-September 2020 with almost 98,000 cases in a day during that period [16]. First Covid-related death was reported in March 2020 and on September 18 of the same year, 1195 reportedly died due to the very reason. Till September there was so sign of decline in the daily number of new cases. Reaching the plateau and subsequent decline then seemed to be a far-fetched dream in the absence of an effective vaccine or drug. On January 4th, 2021, a total of 16278 new cases were detected while 200 deaths were reported country wide. Various models of COVID-19 were put forward to predict the trend yet no estimate had turned out to be even close to the reality.

Officials had claimed that increasing the number of tests would have had helped control the epidemic [17, 18]. Yet they could not provide with any effective strategy for reducing new infections which would have had helped flattening of the national Covid-19 epidemic curve. Several survey results established that a small percentage of the people in the country have had developed herd immunity even though they were unaware of their infection. Thus controlling the epidemic through reaching an adequate amount of herd immunity is a remote possibility. Taking these situations into consideration, public health experts of the country opined and rooted for effective public health measures including evidence-based epidemic control policy to be undertaken unless some safe and effective vaccines were available. As per the suggestions of the authority, testing was increased manifold, resulting in detection of more cases and, increase in treatment and quarantine. But the problem was that all the tests were concentrated in the metropolitan cities and the urban areas. Also a sizable number of cases were asymptomatic or pre-symptomatic; they perhaps unknowingly had spread the infection to others.

An epidemiological study was conducted by ICMR-National Institute of Occupational Health, Ahmedabad, in western India, to assess the distribution of infected cases in the community and whether initial viral load of COVID-19-infected case indicated by cycle threshold (Ct) value of reverse transcription polymerase chain reaction (RT-PCR) could predict about transmission pattern in the community apart from population mobility and its density. The study revealed that only 7% of the infected ones carried high viral load, while another 9% of the infected

population had moderate viral load and rest 84% were carrying low viral loads as per community distribution was concerned [19]. Viral load was categorised as high when cycle threshold value = <24, moderate = 24 to <31 and low = 31 & above (**Figure 1**).

Interestingly, most of the Covid-19 infected cases' clustering happened around the houses of cases, infected with with high viral load. Also, the number of secondary cases was directly related to the increase in viral load. Higher the viral load, more were the secondary cases (**Figure 2**). On an average, each index case with high viral load spread to 6.2 secondary cases, case with moderate viral load spread to 2.7 secondary cases and same with low vial load spread to 0.8 secondary case. Conclusion of the study was that viral load is an important determinant for transmission of Covid-19 infection in the community. It also advised, viral load based segregation of infected cases, with higher (high & moderate) viral load being quarantined away from their families along with contact tracing of all of them for previous 5 days and subsequent screening of the contacts, believing to be an effective strategy to combat the epidemic.

When the country was grappling in the dark, trying to come up with a suitable strategy to contain the epidemic, Ahmedabad COVID Control Model was developed based on previous study findings. The said model appears to be biologically plausible as the same holds true for other infectious diseases too, such as HIV, malaria, leprosy. Tuberculosis etc. Standing up to the expectations, execution of the Ahmedabad Model of Covid Control exhibited a reasonable reduction in the daily number of new cases within weeks of implementation in June 2020. This model of management did not add any extra cost to the existing health care delivery practices for managing COVID 19 cases. In it, Ct value obtained from the RT-PCR machine needed to be mentioned routinely on the all RT-PCR test reports; thereby indicating high, moderate & low viral load, that helped the healthcare personnel assess the transmissibility of the detected cases. It was assumed that on an average 50% reduction would happen which is largely dependent on dedication & motivation of grass root level community health workers, supportive & effective supervision, timely logistic supply of test facilities including contact tracing, timely referral for institutional quarantine etc. Fortunately, the model concerned had some extra added benefits. For instance, if the health care personnel are aware about who all the patients with high viral load are, they would take some extra precaution while dealing with the latter - thereby reducing the chances of infection among the health care providers. The following **Figures 3** and **4** depict the decline & ascent of daily cases in intervention as well as non-intervention areas following initiation of Ahmedabad Model for COVID 19 Control, which was published as an original

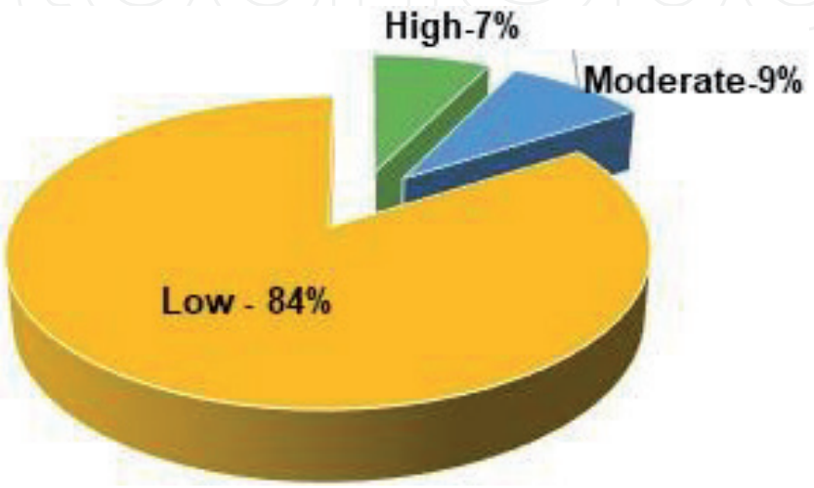

Figure 1.
Distribution of cases with viral load (n = 138) in the studied community.

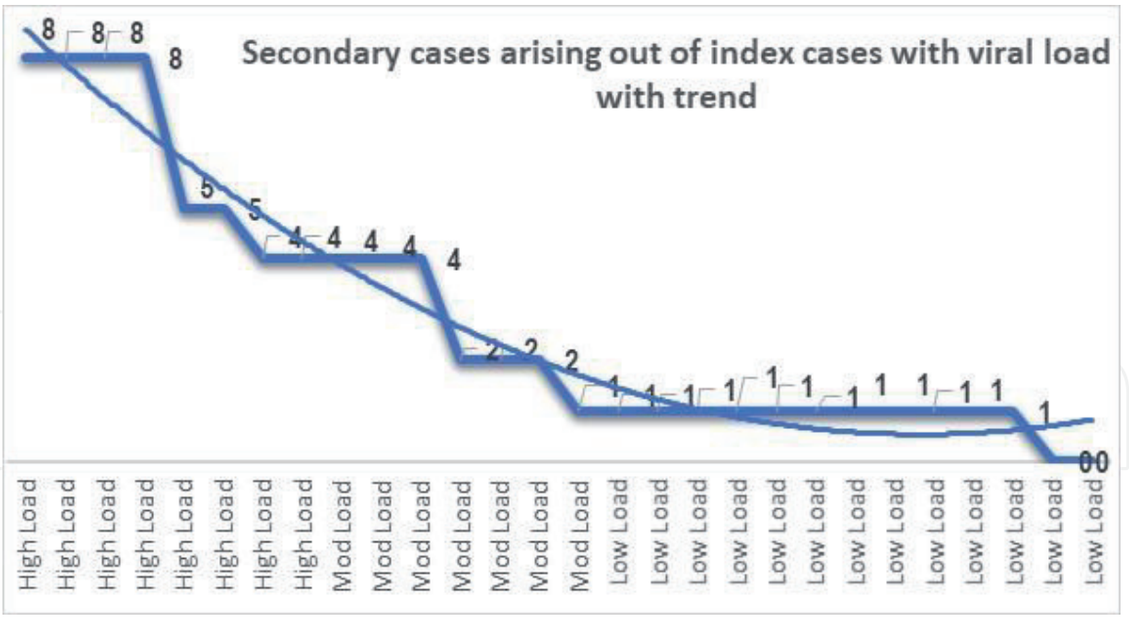

Figure 2.
Secondary cases observed in relation to index cases of high, moderate and low viral load with trend line.

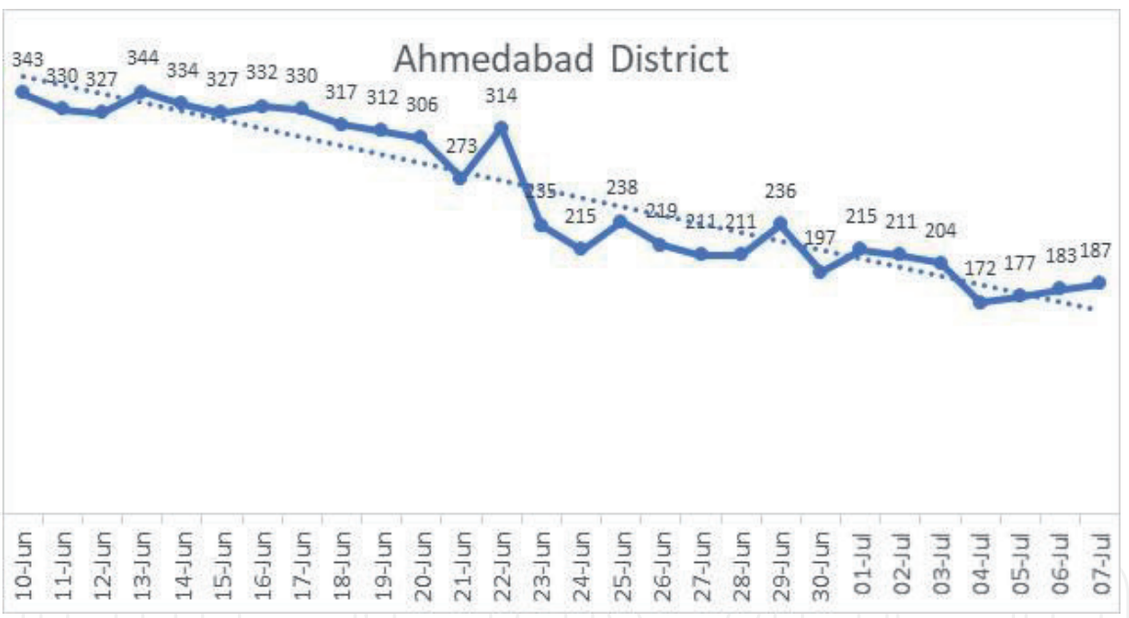

Figure 3.
Daily reported COVID-19 cases in Ahmedabad district 10 June till 07 July.

article titled COVID control strategy – is there any light at the end of the tunnel? in the journal of Family Medicine & Primary Care, 2020; 9:5502-5.

Because of continuous influx of people from UK to India during December 2020 & January 2021, resulting possible emergence of newly detected highly infectious viral strain of Britain in India, Indian Council of Medical Research (ICMR) has instructed various zone-wise Indian laboratories to search for the said infectious Covid 19 strain using cycle threshold (Ct) value of 30 or less considering the fact of their higher infectivity [20]. This again indicates that cycle threshold (Ct) value may be used as a marker of infectiousness or infectivity of Covid 19 transmission. If an appropriate measure is undertaken on time, it can reduce the transmission of cases as was observed in Ahmedabad based study (**Figure 3**), where it was implemented as a method of control.

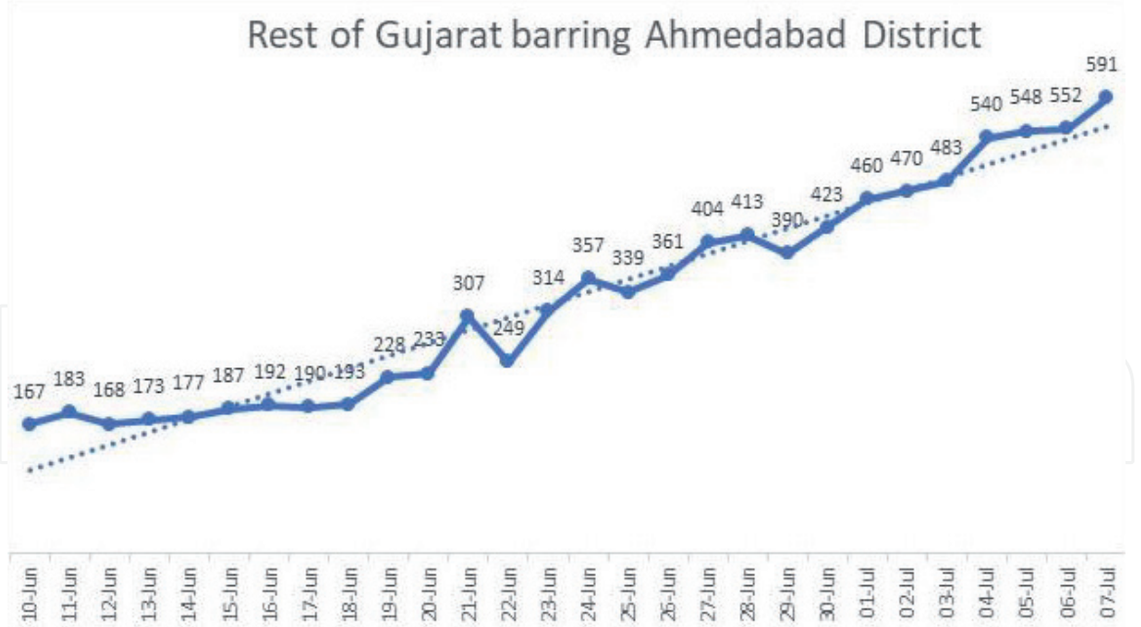

Figure 4.
Daily reported COVID-19 cases in rest of Gujarat State barring Ahmedabad district 10 June till 07 July.

Another study conducted by ICMR-National Institute of Occupational Health, India, showed that viral load is also an important determinant for fomites based transmission too [21]. The study was done on common surfaces such as packaging cardboard and stainless steel surfaces that were smeared with COVID 19 infected materials with known viral load. It showed that fomites contaminated with higher viral load remained infected for a longer period compared to that contaminated with low viral load material. So, viral load is a key factor for the presence of the infectious virus on the surfaces and possibly contributing to the transmission, even after a considerable duration. The viral RNA has higher chances of being identified post-90-min observation period on surfaces contaminated with higher viral load. Therefore surfaces with higher viral load are potentially contagious for longer period as compared to those with lower viral load. The study identified a positive relationship between the viral load of samples used for contaminating the surfaces and viral load of the surfaces post-90-min observation period. The relation was stronger among cardboard surfaces than stainless steel surfaces. A probable explanation can be acquired from the fact that the moist surface of the absorbent cardboard could provide a better harbouring site for viral particles than a non-absorbent surface like stainless steel. The results however partly corroborate with a similar study, where the cultured viral titre was measured over a duration on various surfaces [22]. This study could not suggest the viability of viral particles on the surface but it only assessed the presence of amplifiable viral RNA for specific genes (ORF1ab, in this case). The mentioned study, suggested the viability of these viral particles for over 3 days on these surfaces [21]. The said study was perhaps the earliest from India, to document the relationship between viral load and their detectability on common surfaces. In addition, surfaces with contaminated with relatively higher viral load and with higher absorbability (cardboard) are independently associated with higher risk of COVID-19 retention and transmission. Considering the rapidly evolving literature and experimental procedures, this study was limited by a single sample collection (post 90-minutes observation duration) and did not indicate the viability of viral particle/virion. Further, the results might be extended to emphasise the need for sterilising such fomite surfaces to prevent viral transmission. Considering the positive relation between viral load and the disease contagiousness [19, 23, 24], the sources

(spreader/positive subjects) with high viral load should be treated with great care, i.e., health care facility with possibly high viral load should adopt maximum precautionary measures. The study indicates that fomites could play an important role in the disease transmission in addition to human contact, particularly at COVID-19 care facilities, market places etc. Awareness on fomite-based COVID-19 transmission and the persistence of virion on these surfaces among the health care workers could reduce their risk of contracting COVID-19. Viral load on fomites and the potential role in disease transmission have potential implications in limiting transmission of the recent viral infectious respiratory disease. The above finding has far-reaching public health implications for educating the public in adopting safer behaviour to avoid transmission through fomites. About a fraction of the infected population harbour high viral load and are designated as super spreader which is a matter of great concern [25]. Apart from person to person transmission, the above population would also spread the infection at a much higher rate through fomites unless effective public health controls are undertaken. Similarly, infected cases with moderate vial load would spread the said infection at a moderate rate both by person to person as well as through fomites. Consequently, there should be an effective mass awareness programme using suitable mass awareness education tools by some experienced health care workers. This is more important in places like business areas, shopping malls, market places, tours and travelling, etc., where large gathering occurs with high population mobility and there is every possibility of transmission through fomites apart from person to person spread. So, respective authorities must pay adequate attention to minimise the spread in the above areas as mentioned already.

3. Other factors related to transmission

In Wuhan, China, a novel and alarmingly contagious primary atypical (viral) pneumonia broke out in December 2019. It had since been identified as a zoonotic coronavirus, similar to SARS coronavirus and MERS coronavirus and named COVID-19. As of 8 February 2020, 33738 confirmed cases and 811 deaths were reported in China. Scientists investigated the basic reproduction number (R_0) of the COVID-19 virus considering the fact that R_0 is an indication of the transmissibility of a virus among adjacent population, who are coming in contact to the primary case/s. This investigation found that the estimated mean R_0 for COVID-19 is around 3.28, with a median of 2.79 and IQR of 1.16, which is considerably higher than the WHO estimate of 1.95. The study concluded that the reproductive number of COVID-19 was higher compared to SARS coronavirus. These estimates of R_0 depended on the estimation method used as well as the validity of the underlying assumptions. Due to insufficient data and short onset time as mentioned by the authors, estimates of R_0 for COVID-19 were possibly biased as mentioned in a study [4].

Another study investigated the aerosol and surface stability of HCoV-19 and compared it with SARS-CoV-1, the most closely related human coronavirus. They also looked for the stability of HCoV-19 and SARS-CoV-1 in aerosols and on different surfaces and estimated their decay rates using a Bayesian regression model. The study found that the stability of SARS-CoV-2 was similar to that of SARS-CoV-1 under the experimental circumstances tested. The study concluded saying differences in the epidemiologic characteristics of these viruses probably arise from other factors, including high viral loads in the upper respiratory tract and the potential for persons infected with SARS-CoV-2 to shed and transmit the virus while asymptomatic. The study results indicated that aerosol and fomite transmission of SARS-CoV-2 is plausible, since the virus can remain viable and infectious in aerosols for hours and on surfaces perhaps for days (depending on the inoculum shed).

These findings echo those with SARS-CoV-1, in which these forms of transmission were associated with nosocomial spread and super-spreading events, and they provide information for pandemic mitigation efforts [26].

4. Basic requirements for controlling an epidemic in an area

4.1 Strengthening of inadequate Public Health System

Public Health is defined as a combined system of science & art of preventing diseases, promoting health and protecting lives in a defined geographic area through organised community based efforts. Primary health care is the backbone of public health. Primary health care is an essential health care that should be made available, accessible, acceptable and at a cost that every citizen of the country can afford. Primary health care is based on four principles – Equitable Distribution, Multi-sectoral Approach, Inter-sectoral Coordination and Appropriate Technology. This means resources for improvement of public health infrastructure need to be provided as per felt need of that area; underdeveloped area should receive more resources. In countries with weak public health infrastructure such as India, Bangladesh, Pakistan, Nepal, several African countries among others need their public health strengthened. This means increase of trained human resources (doctors, nurses, public health experts, field workers, etc.), construction of health establishments as per requirements, adequate supply of logistics, storage and transport facilities of vaccines maintaining appropriate temperature, strengthening of immunisation services, strengthening of maternal & child health services, improvement of malnutrition scenario, control of communicable and non-communicable diseases, improvement water and sanitation services etc. Improving all of the above together require an abundance of resources and appropriate planning for judicious usage. Most of the above mentioned countries are not in a position to afford them. Moreover, strong political will appears to be the most important determinant for the said improvement apart from having the resources. Mass awareness is another important issue that helps in generation of demand. Without demand generation by public, things do not move in right direction. A number of social activists, NGOs etc. work to mobilise people to be aware, understand their own needs and generate their demand. Policy makers of the country must be aware of major public health problems of the country so that they can prioritise while developing an appropriate policy for right place at right time. One wrong public health decision will incur heavy cost that the country could have had avoided altogether. Similarly, if an important public health decision is delayed particularly during a public health emergency situation, consequences are increased morbidity & mortality along with other indirect consequences such as loss of job, loss of economy as is being observed in recent COVID 19 epidemic.

4.2 Epidemic preparedness for control of epidemic

4.2.1 Epidemic preparedness team

An epidemic preparedness team comprising an experienced epidemiologist as the chairman, a clinician and a microbiologist as members, is needed to be formed to review the situation of their designated area at regular interval. They need to assess the situation of different regions (based on previous years' situation), the logistic supports needed by them and the services that are necessary for prevention & control of epidemics round the year. They ought to be responsible for arranging necessary training

of subordinate staff that will be required for epidemic control. They should develop a set of guidelines/standard operating procedure including dos and don'ts for use by the health workers while dealing with an epidemic. They are also to be responsible for taking necessary measures for tackling any emerging and re-emerging epidemics well in advance such as establishing an effective surveillance system for early detection, creation of a reliable diagnostic services, constructing temporary shelters for emergency evacuation of affected population during public health emergency if needed etc.

4.2.2 Integrated Disease Surveillance Programme

Integrated Disease Surveillance Programme (IDSP) is an important activity for early detection of an epidemic. Surveillance is defined as the process of continuous collection of required information for necessary action such as prevention & control of diseases. Diseases under surveillance are usually classified into groups. Group A comprises diseases where immediate action is needed (within 24 hour), Group B diseases are less severe where necessary actions are taken usually within a week while Group C are diseases where actions are needed to be taken usually within a month. Continuous collection of information on occurrence of various cases from the entire area are sent promptly at the IDSP office to cover the designated geographical area. Based on the reported case/s from a particular area, necessary actions need to be taken by the designated staff as per need of the situation. This is to be done continuously 24-hour x 7 days, round the year to enable early detection of epidemic with necessary intervention. With the advent of newer technology, surveillance can be strengthened further with the help of drones, mobile phone based applications, electronic communication system etc. to collect information from the remote areas.

4.2.3 Regular analysis of data with epidemiological interpretation to assess the situation

Regular analysis of data with epidemiological interpretation is an essential component for early detection of epidemic in an area. Various soft wares are available and used for this purpose such as SPSS, Strata, Epi Info etc. If there is an evidence of existence of epidemic prone case(s) with tendency to increase compared to occurrence of them earlier, it must be brought to notice of IDSP authority/Epidemic Preparedness Team for immediate action/control measures. An all-time functional alert system needs to be generated to alert the authority whenever such a situation arises. This will help detect an epidemic at its early stage. Since timely intervention can reduce the damaging effect of an epidemic to a great extent, detection of an epidemic at its early onset is of utmost importance.

4.2.4 Early and prompt action for containment of epidemic immediately on detection

On receiving information, the epidemic investigation team must move to the spot immediately to verify the existence and magnitude of problem. Steps are needed initially towards controlling epidemic with verification of diagnosis and confirmation of epidemic. Diagnosis may be confirmed by isolating organism from the biological samples collected from the few cases from the affected area. If necessary, required assistance from a nearby laboratory may be sought for isolation of organism and confirmation of diagnosis with the help of microbiologist/virologist present in the epidemic investigation team. Confirmation of epidemic is done by comparing data of present situation with that of previous years. If it is clearly in

excess (>2 standard Deviation of average number of cases of previous 3 years), epidemic is confirmed. Once epidemic is confirmed, rapid searching of cases is needed by house to house visit through health workers for further management. While visiting houses and identifying cases, relevant information is collected using a relevant questionnaire to assess the possible source of infection. Once the source(s) are identified, every attempt is to be made to break the chain of transmission, so that epidemic starts to subside. Searching of more number of cases should continue in the community till cases cease to occur. Whenever new cases are identified, they need referral to appropriate health centre for further management. Disposal of infectious material must be taken care of to avoid further spread.

4.2.5 Development of suitable strategy based on felt needs

An important action is making the community aware about the disease, its prevention measures, dos and don'ts, etc. Handling the media is an important aspect since rumours about the disease cause unnecessary panic. Epidemic team members will remain at the spot till epidemic subsides with regular communication to their coordination centre and higher management authority for necessary guidance and support.

4.3 Diagnostics, therapeutics and prophylactics using biotechnology for control of COVID 19

COVID 19 pandemic is complex problem, which needs trans-disciplinary studies. The development of medical biotechnology to produce pharmaceutical and diagnostic products is a need, which needs close collaboration with other disciplines. It should be emphasised that it has been clear that coronaviruses know no borders; therefore, border-less solutions are needed to fight COVID-19. Hopefully the lessons we learned from SARS-CoV-2 will help us to prevent possible pandemic in the near future. Regarding development of diagnostics, one of the crucial factors for control of epidemic is rapid and reliable detection of infected cases with some indication about assessment of its infectivity, if possible. A number of experts across the world have been trying to develop various kits, various machines for use of those kits for detection of causal organisms using various principles of biotechnology. Certain aspects need to be considered while developing kits & related items such as test results must have high sensitivity and high specificity apart from low cost, less time taken, user friendly technique that can be used by peripheral health workers without much fuss. Similarly, in therapeutics, one needs to develop low cost and efficacious drugs or other intervention agents targeting virus entry in the body, multiplication and rapid clearance from the body with minimum side effects.

Since it has been established that viral load is an important determinant for transmission of COVID 19 in the community, hence viral load may be considered an important factor of infectivity. Hence, rapid antigen detection kits that are being developed by various agencies for detection of COVID 19 may contain some indicator for assessing viral load or infectivity. Thanks to biotechnology, addition of indicators is possible and innovators must make sincere efforts towards that as it would help better control of epidemic caused by COVID 19, which was observed in Ahmedabad COVID control model.

4.3.1 Immunity

Following a natural infection, immunity develops through a series of processes that typically takes some time over 1 – 2 week. Human body normally

responds to a viral infection immediately with a non-specific innate response in which macrophages, neutrophils, and dendritic cells slow the progress of virus and may even prevent it from causing symptoms. Non-specific response of this kind is usually followed by an adaptive response where the body makes antibodies that specifically bind to the virus. These antibodies are proteins called immunoglobulins. This is known as humoral immunity and B cells of our body are responsible for this process. Human body also makes another groups of cells called T-cells that recognise and eliminate other cells infected with the virus. This is called cellular immunity. Following this, virus may be cleared from the body by combined adaptive response, and if the response is strong enough, may prevent progression to severe illness or re-infection by the same virus. This process is often measured by the presence of antibodies in blood [27]. If a sizable portion of the community population (60 – 70% or more) get infected with COVID 19 infection, it is expected that most of them will develop antibody against COVID 19 infection. Some of the so called uninfected population will also develop antibody against COVID 19 virus, most likely due to subclinical or asymptomatic infection. If their antibody is able to prevent reinfection, it is known as herd immunity or community acquired immunity. Since the disease is new, community-based sero-survey for COVID 19 antibody and its titre can only tell us with certainty whether it is protective against reinfection or not. Similarly, if the cohort is followed up longitudinally with repeated sero-surveys for assessment of antibody titre, duration of protection would be ascertained. It is interesting to know that some of the naturally infected persons do not develop antibody following COVID infection.

4.3.2 Vaccination against COVID 19 Infection

Vaccination is a powerful tool for prevention/control of an epidemic provided it is safe, having a high protective efficacy and given in appropriate time. It is usually used for primary prevention which means it needs to be given before exposure to the infectious agent and occurrence of the disease. Across the world, several types of vaccines are being developed with the hope of combating the COVID-19 pandemic. Yet all the vaccines have the same primary impact - they stimulate the immunity system of the vaccinated individuals to grow memory B cells and T cells against the SARS-CoV-2 virus. These very memory B-cells and T-cells will protect the individuals against subsequent and serious Covid-19 infections.

Vaccination with the first dose will mimic a primary immune response similar to that of being exposed to the virus for the very first time. Mild symptoms of the infection may appear as the immune system gradually develops antibodies against the virus concerned. As a result, if the person is exposed to the virus again or if the subject receives a second dose of vaccine, his or her immunity will flare up and develop what we call a secondary immune response. Initial memory cells get activated. This secondary immune response is faster and much stronger when compared to that of the primary response. This manifests as elevated concentrations of antibodies and higher counts of T-cells. These together help in getting rid of the virus rapidly and thereby prevent occurrence of symptoms, severity and morbidity related to Covid-19. The individual, thus will have more memory B and T cells generated in his or her body; therefore, will have strong immune memory of the Covid-19 virus. It is this immune memory of the individual that will help him or her battle against the infection.

Vaccination and immunity development can be categorised into two types: ACTIVE IMMUNITY and PASSIVE IMMUNITY.

4.3.2.1 ACTIVE immunity

DNA Vaccines, RNA Vaccines, Viral Vectors, Viral Sub-units, Live Attenuated, Inactivated Virus, VLP or Virus-Like Particles, Split Virus Vaccines, RNP (Ribonucleoprotein) Vaccines.

4.3.2.2 PASSIVE Immunity

Antibodies (MONOCLONAL and POLYCLONAL), Convalescent Serum, mRNA induced Antibody.

Considering the chaos and the panic this pandemic has ensued, developing vaccines and immunising the population as soon as possible, is of immense importance - especially folks belonging to high risk groups, vulnerable groups and pockets that have been badly affected by this infection. This would help contain the disease and reduce not only spreading of the infection but also the morbidity and mortality associated with it. Thus vaccines happen to be an important tool in public health control of pandemic and epidemic. Substantial research is being undertaken to develop effective vaccines that would help check the disease spread adequately.

Since in a highly populous country or in resource poor setting, availability of vaccines may not be adequate compared to its number of recipients, particularly in the beginning, certain categories of people may be considered for immunisation on priority basis depending on country's situation:

a. Health care personnel

b. Essential workers such as law & order maintenance workers (police personnel)

c. Patients with comorbidities like Diabetes, Hypertension, Bronchial Asthma

d. Subjects over the age of 65 years

e. Street residents and slum dwellers

Manufacturing agency such as PFIZER and MODERNA have been working to develop mRNA Covid-19 vaccines where genetically sequenced spike proteins of COVID 19 virus is injected in body as vaccine and molecules of the virus' messenger RNA will be recognised and targeted by our immune systems as the antigen. Then the immunity system will get triggered enough to produce antibodies against the said virus [28].

Serum Institute of India, Pune has teamed up with British-Swedish OXFORD-ASTRAZENECA to launch *COVISHIELD* in India. It is a viral vector vaccine where viruses are being modified to hold the target pathogen and then these modified organisms are administered via the vaccines. These in the human body, will initiate and develop immunity against covid-19. Chimpanzee Adenovirus is being used to deliver the corona virus antigen in this SII vaccine. Participant enrolment and vaccination of Phase III Human Clinical Trial COMPLETED [29].

COVAXIN - Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) is India's indigenous Covid-19 vaccine and is being developed by India based manufacturing agency, BHARAT BIOTECH, in collaboration with ICMR - National Institute of Virology, Government of India. It is in its Phase III Human Clinical Trial. *ZyCoV-D* is a plasmid DNA vaccine being developed by ZYDUS CADILA, another Indian manufacturing agency and is on its Phase II Human Clinical Trial [29].

SPUTNIK V - DR. REDDY'S LABORATORIES LIMITED [Russian and Indian collaboration] and SPUTNIK LLC are jointly conducting Phase II Human Clinical Trial to assess safety and immunogenicity of Gam-COVID-Vac combined vector vaccine [29].

Biological E. Limited has developed a vaccine and is conducting studies to assess the safety, reactogenicity and immunogenicity of the vaccine containing Receptor Binding Domain of SARS-CoV-2 for protection against Covid-19 disease when administered to healthy volunteers on days 0 and 28, intramuscularly [29].

COVISHIELD has demonstrated efficacy of 70.4% against symptomatic Covid-19 and 100% efficacy against hospitalisation due to severe Covid-19. The Sputnik vaccine has demonstrated 92% efficacy. According to FDA, the Moderna vaccine was 94.1% effective at preventing symptomatic cases. The Pfizer vaccine has claimed 95% effectiveness.

The mentioned vaccines have undergone/are undergoing immunogenicity, efficacy and safety trials in 18 Years and above and hence will be allowed to be used in adults under "Emergency Use Authorisation." Only Pfizer's vaccine was authorised for people ages 16 and up in USA. Trials are underway for age group 12-18 and in due course of time the vaccines may be allowed to be used in this age group. Also no conclusive study in pregnant women have been conducted - so safety during pregnancy cannot be ascertained yet. Since surveys have not been conducted to establish the need or the lack of need for vaccines in individuals who already have had the disease, these recovered individuals may be considered last for vaccination.

As seen till now, one would require to get two shots of the same vaccine - 0.5 ml each dose, to attain a desired level of protection. The 2 doses Moderna and Covishield are to be taken 28 days apart while the 2 doses of Pfizer and Sputnik V are to be taken 21 days apart. Usually it takes about 14 days for the antibody formation but the mRNA vaccine of Pfizer has demonstrated response as early as 10 days after the 1st dose. One should remember two shots of the vaccine is not enough to protect one completely. Covid-19 is a brand new disease; the scientists, doctors, society and humankind are all learning more about it as days pass by. A vaccinated person most likely will not develop the disease or be severely ill but he may get infected if hand hygiene, respiratory hygiene, physical distancing and proper mask usage are not maintained. And if infected, chances of him spreading the infection will increase manifold. Therefore, it is important to follow the rules of the new normal even after vaccination.

4.4 Research to explore effective mechanisms to contain at an affordable cost

More operational and translational research works are needed to explore alternative control mechanisms such as newer diagnostics, therapeutic and prophylactic agents at an affordable cost. We also need to have various environmental measures where virus does not survive or virus transmission chain could be broken using bio-technology principles. Personal protective devices such face masks, various hand hygiene devices, disinfection devices may be made using novel techniques without major health hazards based on bio-technology principles. Disposal of used face masks, many of which are made of synthetic/non-bio-degradable materials is a threat to our environment. Hence suitable material that are bio-degradable and at the same time protects from virus without hampering oxygen supply to our body should be thought of. Suitable disinfection devices for disinfecting used non-disposable/re-usable items of health care personnel is needed particularly for rural health system of developing countries. Mobile van fitted with disinfection devices using engineering expertise along with bio-technology skill could be helpful as it could cover a number of health centres in a day for disinfecting their used items.

Necessity is the mother of invention – appears to be true as it is observed that many medical, engineering and bio-technology students are coming up with brilliant and innovative ideas for interrupting COVID virus transmission. Innovations of this kind must be encouraged.

5. Suggested measures for controlling an epidemic of COVID 19

One needs to understand about how an imported epidemic starts and progresses its course as time passes by. Based on our understanding it may be categorised as:

1. Stage I: Imported transmission - Initially cases occur only in people return from foreign countries, foreign visitors came to a country for business or tourism purpose etc. and their contacts.

2. Stage II: Cluster transmission – The disease spreads from above infected group to nearby local population usually confined to smaller geographic area where source of infection is by and large traceable.

3. Stage III: Community transmission – A large number of people are infected simultaneously in different parts of the area within a large geographic area and where source of infection is not identifiable for a large section of population

4. Stage IV: Declined and low level transmission – When epidemic curve declines after reaching plateau but cases still continue to occur in areas at much lower level involving relatively fewer populations.

It may be noted that incubation period of COVID 19 infection ranges between 2 to 14 days with an average incubation period of 5–7 days. Maximum colonisation of virus occurs in oropharynx and naso-pharynx on second or third day from the onset of symptoms of an infected person. Hence maximum chance of transmission of virus from an infected person in his/her early days following development of symptoms. As a result, chance of transmission is relatively higher following detection by RT-PCR (considering the fact that patient usually comes on second day following onset of symptoms), when there is an opportunity of intervention. If that opportunity is missed, infection will keep on spreading in nearby population. On the other hand, it is easily understood that an epidemic is easy to control if it is detected early when very few people are affected. In the event of any delay in detection and/or lack of required intervention at the beginning due to any reason, the community/country needs to pay a heavy price for that. COVID 19 epidemic is the best example of it in recent time. Apart from direct consequences of high morbidity and mortality, indirect consequences are havoc such as downfall of country's economy, loss of jobs, loss of wages, poverty, starvation leading to malnutrition, increase of mental diseases etc. It may be kept in mind that because of high global population movement, any infectious disease with pandemic or high epidemic potential, it may spread to people of other parts of the world with the passage to time unless strict vigilance and control activities are undertaken rigidly.

COVID-19 test detects genetic material of the virus using a laboratory technique called real time RT-PCR reaction (Real-Time Reverse Transcription – Polymerase Chain Reaction). RT-PCR testing can tell us whether there is a detectable virus present in an individual. Still, it does not accurately tell us whether that individual is infectious or is capable of spreading the disease. Cell culture is the standard technique for determining whether a patient is contagious or not. In the absence of

viral culture data, one can use viral load or cycle threshold (Ct) values derived from RT-PCR as a proxy for the likelihood of transmission. RT-PCR is a sensitive technique for mRNA detection and quantification currently available. It is a laboratory technique facilitating reverse transcription of RNA into DNA and amplification of specific DNA targets using polymerase chain reaction (PCR). It primarily wants to measure the quantity of a selected RNA. This is achieved by the amplification reaction using fluorescence, a way called real-time PCR or quantitative PCR (qPCR). Combined RT-PCR and qPCR are routinely used for analysis of organic phenomenon and quantification of viral RNA in research and clinical settings. Compared to the two other commonly used techniques for quantifying mRNA levels, Northern blot analysis and RNase protection assay, RT-PCR wants to quantify mRNA levels from much smaller samples. In fact, this system is sensitive enough to enable quantitation of RNA even from one cell. In a real time PCR assay a positive reaction is detected by accumulation of a fluorescent signal. The Ct (cycle threshold) is defined as the number of amplification cycles required for the fluorescent signal to cross the limit (i.e. exceeds set detection level). In other words, The Ct is the number of replication cycles required for a signal of RT-PCR product to cross a determined threshold. Ct values are inversely proportional to the quantity of target nucleic acid within the sample (i.e. the lower the Ct level the greater the quantity of targeted nucleic acid within the sample).

Considering above, it appears with reasonable certainty that viral load during early infection is an important determinant for transmission in the community by various routes including fomites based transmission. If viral load is high, chance of transmission is higher among nearby susceptible population with lack of proper precaution. Medical fraternity caring COVID 19 patients must take it seriously as many of the patients attended by them are with higher viral load with increased transmission potential and any lapse of precautionary measures on their part would make many of them infected as was observed in several countries. It is understood that virus multiplication occurs within first few days inside the body of an infected person. Antiviral agents such as Remdesevir may be beneficial not only for the patients but also for the attending health care personnel as it helps in reducing transmission to them by reducing viral load if given early in the disease. It is understood that there is hardly any benefit if anti-viral agents are given in late phase of the disease.

It is now evident that magnitude of viral load may be obtained easily from RT-PCR test of a COVID 19 positive case without any extra cost. More the cycle threshold (Ct) value, lower is the viral load (inversely related). Similarly, lower is the Ct value, higher is the viral load. Any Ct value of 35 and higher is considered as non-infectious although infected. Similarly, Ct value of 20 or below may be considered as highly infectious with higher transmission potential. Recently a number of qualitative COVID 19 detection kits are available in the market (such as rapid antigen detection kit) that does not indicate Ct value based viral load. Further studies are required to add viral load assessing facility in those rapid antigen detection kits for assessing infectivity of an infected case. Apart from viral load, it is now obvious that transmission will occur if favourable conditions are available such lack of protection measures, population density, population mobility, lack of awareness about the disease etc. So, mass awareness is an essential component of any public health control measures.

It is a fact that many countries in the world do not have an effective public health infrastructure such as required number of doctors, nurses, field workers, health technicians etc. as per WHO set guidelines, required number of various tiers of health establishments such as primary. Secondary and tertiary level of health establishments, diagnostics facilities, cold chain maintenance facilities and epidemic/infection control policy & strategies etc. Unless proper logistics supports

are available, vaccination is not possible even if it is made available. Hence, prevention of occurrence of cases much before it turns to an epidemic proportion should be a better choice. Appropriate infection control policy with an effective infection control strategy must be made available with experienced public health experts.

To summarise, COVID control strategies may include (based on already established evidence) the followings:

1. Viral load indicated by Ct value could be used as an indicator of infectiousness of an infected person. Cases with high and moderate viral load must be kept away from the family/community even if they are asymptomatic or mildly symptomatic to avoid further transmission particularly in under-privileged areas, rural and slum areas.

2. Ct value based segregation identifying higher infectious cases along with contact tracing of them of previous 5 days appears to be an effective strategy as was observed in Ahmedabad Covid 19 infection Control programme.

3. Health care workers need to know their patients' Ct value on admission to hospital/health centre to enable them to remain more careful about the transmission potential of patients.

4. Effective implementation of it in primary health care set up would better utilise country's rural public health infrastructure.

5. Asymptomatic and mild symptomatic cases with low viral load may be kept at home with standard precaution.

6. Moderate and severe symptomatic cases need to be referred to Covid hospital for further management.

Home quarantine for cases with higher viral load is expected to facilitate intra-familial transmission of COVID 19 cases in other family members, hence it is not suggested. On the other hand, same with low viral load may be quarantined at home with standard physical distancing, hand hygiene and face mask. Presently COVID 19 epidemic is largely concentrated on 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 in coming days since 60 to 70% of developing country's population reside in villages. Considering 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. This will also reduce hospitalisation of cases & deaths and help improving bed availability, thereby better utilisation of public health infrastructure would be possible. Extensive community awareness about prevention & control of COVID 19 infection along with role of viral load. Ct value is essential for that. One needs to remember that success of Ct value based segregation will largely depend on dedication and motivation of grass root level field workers. If they work sincerely with supportive supervision by their immediate supervisors and higher leaders, cases are expected to decline soon, leading to control of epidemic. Proper training of various categories of health workers as well as logistic support must be in place. Moderate to severe symptomatic persons need to be referred to nearby hospital/health centre for management of COVID 19 infection. Asymptomatic and mild symptomatic may be sent to home or institutional quarantine as per their reported viral load as mentioned already.

We need to understand that to control an epidemic with high transmission potential such as COVID 19, multiple strategy based attacks are needed to break the all possible transmission chains. Vaccines whenever possible must be considered in addition to other public health measures. Safety & protective efficacy must be assured of a vaccine before going for mass vaccination in a community. Since the disease is new and vaccine(s) are also new, continuous monitoring & supervision of the recipients of vaccines are needed. Cases with vaccines failure must be identified early for their alternative protection against this disease. Detailed epidemiological information may be collected about possible factor/s that are associated with vaccine failure. Since, COVID 19 is originated from RNA virus, frequent genetic mutation is possible over a period with consequent changes of its virulence and also its epidemic transmission potential. Herd immunity may be another important factor that develops from earlier infection or due to vaccination to a section of population of the community. Monitoring of above issues from time to time will be helpful for taking a judicious decision about vaccination strategy for a particular community. It may also be noted that most epidemics undergo a natural decline as time passes by, irrespective of intervention measures undertaken or not. That does not mean that intervention is not important as delay in intervention measure increases morbidity and mortality. Last but not the least, there is no single strategy or a straight forward pathway to control the epidemic. Rather it is a diversified and complex mechanism which is based on various situations and interplay of agent, host and environmental factors. A judicious planning, timely intervention and efficient management with required logistic support services can reduce human sufferings to a great extent.

Lastly, it was observed that an overall 35% (21 out of 60) asymptomatic infected cases got detected while doing contact tracing in a community based study in western India (unpublished data). The magnitude of asymptomatic cases was higher with cases of low viral load (46.6%), whereas it was about 20% with cases of high viral load. Asymptomatic cases of higher viral load would spread the disease at higher rate, similar to that of symptomatic cases. Hence, precautionary measures such as hand hygiene, face mask, physical distancing etc. are extremely important and required to be practiced by all considering the fact that everyone around us is potentially infected and could transmit the disease. So, community people need to be educated about transmissibility of asymptomatic infection and about ways of its prevention. Similarly, awareness about safe disposal of their used items considering the possibility of transmission from them is equally important too.

6. Continuous vigilance for variant of mutant strain of COVID 19 if any

Recently, mutation of SarsCov2, namely N501Y, has been reported in the United Kingdom and linking it to further increased transmissibility. It is a matter of great concern, especially at a time when the emergence of vaccines has brought joy and expectation for the mass population. The new UK strain designated as VUI2020/12/01 (variant under investigation, year 2020, month 12, variant type 01) has recorded over 20 mutations, mostly silent, causing no change in the protein. Biologically, mutations represent steps in virus evolution under selection pressure of the host immunity. Scientists view these as a process evolved by the virus to escape immunity or to enhance transmissibility. As the virus replicates, mutations happen in its genes continually through a process called “antigenic drift”, causing minor changes in the surface protein. However, changes of this kind could accumulate over time, and result in newer viruses that could become antigenically different such that the existing antibodies mounted by the host immune system to the original virus fail to recognise and neutralise them [30].

Scientists wish to have the answer about mechanism of these mutations and whether there is a role for host immunity in driving them? More importantly, could antibody treatment or other therapies have an influence in the process? The preprint of a recently submitted paper to medRxiv portal by the group in Cambridge, UK, led by Dr. Ravinder Gupta, has focused exactly on these issues [31]. The above study is based on a single case report of an immune compromised individual with chronic SARSCoV-2 infection, lasting over 100 days and treated with three units of convalescent plasma, two on day 65 and one on day 95 in an effort to neutralise the virus and treat the chronic infection. The virus was detectable in all his nasal swab samples collected at least 23 times over a period of 101 days, despite the plasma therapy. The authors investigated the SARS-CoV-2 evolution and found important changes in its genome caused by two new mutations in the spike protein, one a deletion of AA Histidine and Valine at positions 69 and 70 and, two, one AA replacement at position 796 (D796H). The authors state that while the two mutations did not increase infectivity of the virus, these might have been responsible for decreased sensitivity of the patient to convalescent therapy. Since it is a single case report, the results of the study is not generalizable. But, it raises an important issue of generation of "escape mutants" of the virus in patients with persistent infection. The virus escaped attack by neutralising antibodies present in the convalescent plasma. Continuous vigilance of such newer strains is needed particularly for both their transmissibility and potential to evade vaccine-mediated immunity. The emergence of new mutants of the coronavirus further emphasises the need for observing infection-control practices even more strictly and until the protective herd immunity is developed.

Epidemiologically, continuous collection of pertinent information is required to look for evolution of any variant or mutant strains over a period particularly with higher virulence and more destructing effect to human. Investigation facilities such as ability to perform genetic sequencing for matching newer strain with original virus is needed to identify them. It is obvious that earlier the detection, better actions to control the epidemic is possible. Finally, we wish to conclude that Ahmedabad COVID Control Model appears to be an important evidence in documenting the purpose of this chapter [32].

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