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Research Article

Rapid fall in Active cases of COVID-19 in Indian Territory of Lakshadweep Further Confirmed the Existence of A Long Term Non-Specific Immunity in the Population that protected against Severe COVID-19 with decreased Mortality

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Abstract: The SARS-CoV-2 virus, the causative agent of COVID-19, has become a formidable enemy to mankind for its ability to quickly mutate & evade the immune system of the host. We have reported earlier that the territory of Lakshadweep in India reported the first case of COVID-19 in January, 2021 long after its invasion in the other states of the country. And following its first appearance, there was gradual spread of the disease in the population which was waning by the end of March, 2021. The waning of COVID-19 was attributed to prior immunization of the population with MMR (Mumps Measles Rubella) vaccine. In this article we have continued the study until July 31, 2021 and a significant observation was that after a pause in the number of COVID-19 cases, there was an increase in number of confirmed & active cases of COVID-19. However, an abrupt fall in the number of active cases of COVID-19 followed and by six months there were insignificant number of active cases of COVID-19. Significance of these observations has been discussed in this article.

Key words: COVID-19 – SARS-CoV-2 - Active case - MMR Vaccination-Immunity

INTRODUCTION

Ending the current COVID-19 pandemic and preventing recurrence requires vaccines that could provide long-lasting immunity against the causative virus, SARS-CoV-2. To achieve this goal, an effective vaccine is required to elicit both CD4+ and CD8+ mediated T-cell immunity, in addition to the production of neutralizing antibodies by B cells. However, the present regimen of vaccines predominantly produces neutralizing antibodies which may not provide long lasting protection against SARS-CoV-2 virus.

However, it has been assumed that immunological status of a population may play an important role in preventing or slowing down the spread of the virus in the population. In that context, it was noted that some populations are more vulnerable to the SARS-CoV-2 virus resulting in high mortality from COVID-19. In a series of papers, we have demonstrated earlier that populations having prior immunization with different pathological microbes had a profound effect on the spread of COVID-19 in the Indian population^[1-7]. In our recent study with data from a cluster of eight states, showed a marked decrease in the number of confirmed COVID-19 cases following Lockdown with the exception of Union Territory of Lakshadweep, where no confirmed cases of COVID-19 was recorded until December, 2021. While exploring the plausible cause for this uncharacteristic resistance against the development of COVID-19 for ten months and more since its first appearance in the country, we found that it was probably due to existence of strong underlying immunity in the population against SARS-CoV-2 that could have developed due to prior immunization with MMR vaccine^[8].

The region of Lakshadweep has a history of vaccination/immunization against various pathogens which included Rubella, measles etc. One of the world's largest vaccination campaigns against measles and rubella was launched in February 2017 in Lakshadweep and some other states by the Government of India. Under the Measles-Rubella (MR) campaign, all children in the target age group (between 9 months and less than 15 years) were given a single shot of MR vaccination, irrespective of their previous measles/rubella vaccination status or measles/rubella disease status with the anticipation that the additional campaign dose would boost the already existing immunity in the subjects and thereby protect the entire community by eliminating transmission of measles and rubella and plausibly from other related viruses. There are recent studies showing antibody titre to MMR virus was significantly higher in those who had confirmed COVID-19^[10,11]. In this article, the study in Lakshadweep has been extended until complete waning of active cases of COVID-19 in the population and the plausible significance of the results obtained has been evaluated.

METHODS

The present study was carried out on the data collected on COVID-19 from different sources that included the Ministry of Health, Government of India (web site at www.mygov.in); Health bulletin of Government of India and from other National and International News outlets. The raw data used in this study were from the month of January, 2021 when first case of COVID-19 was reported in Territory of Lakshadweep, to July 31, 2021. The Statistical analysis was performed by Microsoft Excel and power point programs and the correlation studies were performed using web based Pearson Correlation Coefficient program. The data was considered significant when p value was less than 0.05.

RESULTS AND CONCLUSIONS

Briefly stated that more than two month long 'Lockdown' was imposed on March 25, 2020 to control the spread of COVID-19 in all regions of India. Following the end of complete Lockdown on 31 May,

2020, the Lockdown was gradually relaxed in a phased manner of ‘one month’ with some restrictions being maintained in some sensitive ‘COVID-19 pockets’ in the population. The implementation of Lockdown had a positive impact on limiting the progression of COVID-19 in the entire population [1-6], with no cases being recorded in the Union Territory of Lakshadweep until December, 2020. The first case of COVID-19 was recorded in later part of January, 2021. However, from the month of March, 2021, a second wave of COVID-19 started all over the country and the island of Lakshadweep was also affected. In our earlier study, it was reported that the first case of COVID-19 was detected during 3rd week of January, 2021 and henceforth the total number of confirmed cases of COVID-19 showed an increase in volatility. However, the number of active cases of COVID-19 gradually subsided by March 31 and interestingly no mortality was recorded from COVID-19^[8].

In this article, an extension of our previous study, it was observed that following a pause, there was a gradual increase in the number of confirmed cases of COVID-19 which continued until June, 2021. However, the curve gradually flattened. The **Figure 1** reflects the distribution of COVID-19 in Lakshadweep from 20 January, 2021 until 31 July, 2021. It was clear from the graph that the actual number of confirmed cases of COVID-19 increased in linear fashion until middle of May, 2021 and thereafter it made a small peak and gradually flattened. There was a tendency of making a ‘S’ curve but it was incomplete signifying no further acceleration in number of COVID-19 cases. And the curve bucked the predicted trend line of confirmed cases (p value ≤ 0.01). The prolonged flattening of the curve from beginning of July, 2021 was encouraging. This observation was further supported from the data of active cases of COVID-19 in the population.

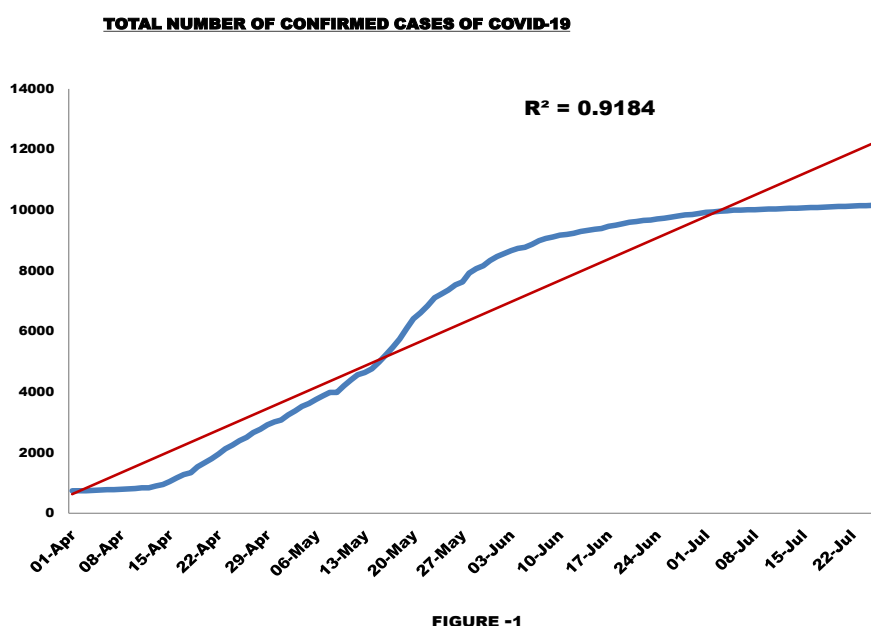


Figure 1: The total number of confirmed COVID-19 cases in the Union territory of Lakshadweep showing a flattening of the curve which was consistent until 31 July, 2021.

Such initial increase in number of COVID-19 cases in the population followed by flattening of the curve plausibly suggests a prior history of immunization in the population. As discussed elsewhere, the late onset of COVID-19 in Lakshadweep was probably due to prevalence of immunity in the population from prior vaccination with MMR vaccine^[8].

However, as we have shown earlier that the percent change in the number of COVID-19 cases in the population serves as a better indicator of the progression of the disease in the early stages as it accounts for the volatility of the disease in a population^[3]. In the present study, the percent change of COVID-19 in the population demonstrated a consistent downward trend in progression of the disease from the beginning (**Figure: 2**). After showing an initial volatility, the rate of progression of the disease stabilised from 22nd March, 2021 and thereafter remained flat until July 31, 2021, with the trend in progression of COVID-19 being not significant.

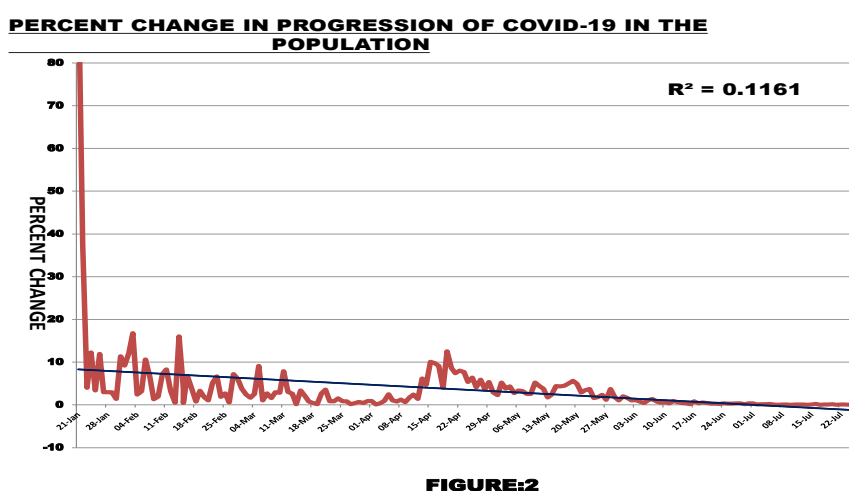


Figure 2: The percent change of COVID-19 in the population showed a downward trend with initial volatility. The trend line and actual progression was identical, showing a consistency.

In order to assess the impact of COVID-19 in the population, the number of active cases of COVID-19 was assessed. As observed and reported elsewhere, the first active case of COVID-19 in the population in Lakshadweep was recorded on 2nd February, 2021^[8]. In this study, the total number of active cases in the population from 2nd February, 2021 to July 31, 2021 is depicted in Figure: 3. It was interesting to note that when the second wave with high number of active cases was clearly visible in rest of the country, the active cases had just started to be visible in the population of Lakshadweep. The first peak in the number of active cases was made around 12-13 March, 2021 and thereafter the number declined as reported earlier^[8].

However, it was observed that following maintaining a low number of active cases in the population, there was a sharp rise in the number of active cases from middle of April reaching a peak around 13 May, 2021 (2nd wave). This rise in the number of active cases was accompanied with an abrupt increase in mortality rate of COVID-19 in the population. Following the peak in the number of active cases, there was an abrupt & rapid decline in the number of active cases of COVID-19 in the population reaching a nadir by the middle of July, 2021. Thereafter, the number of active cases was maintained a base level, as observed prior to 30 March, 2021. Interestingly, it was observed that within a span of only six months two peaks in the number of active cases were made, which declined rapidly reaching a base level by the end of July, 2021 (**Figure:3**).

Due to the rapid rise and wane of active cases within a short period of time the trend line showed low R^2 value which was non-significant.

The data validates our previous hypothesis that existence of prior immunization (with MMR) in the population of Lakshadweep played a significant role in rapid control of infection by SARS-CoV-2

virus. Consistent with this data, the correlation study between the number of active cases and the number of confirmed cases of COVID-19 was not significant as shown in Figure: 4. This data implied that most individuals infected with the virus, SARS-CoV-2, did not progress to active stage of COVID-19, subsequently recovered completely from the disease.

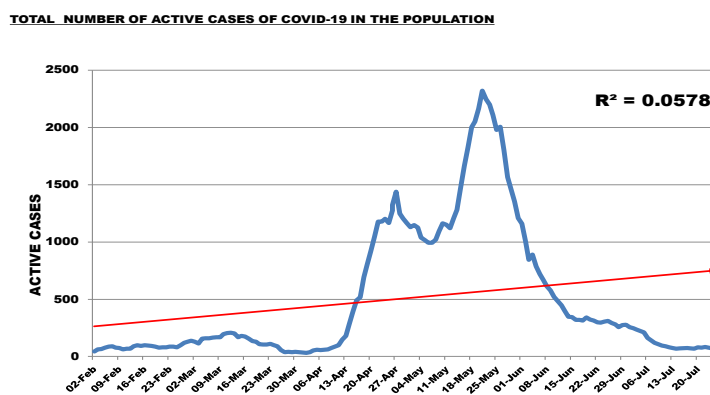


FIGURE-3

Figure 3: Total number of active cases of COVID-19 in Lakshadweep demonstrated a rapid fall in number of active cases of COVID-19 after initial rise. The overall trend registered a non significant rise of active cases with $R^2 = 0.057$.

CORRELATION OF ACTIVE CASES AND CONFIRMED CASES OF COVID-19

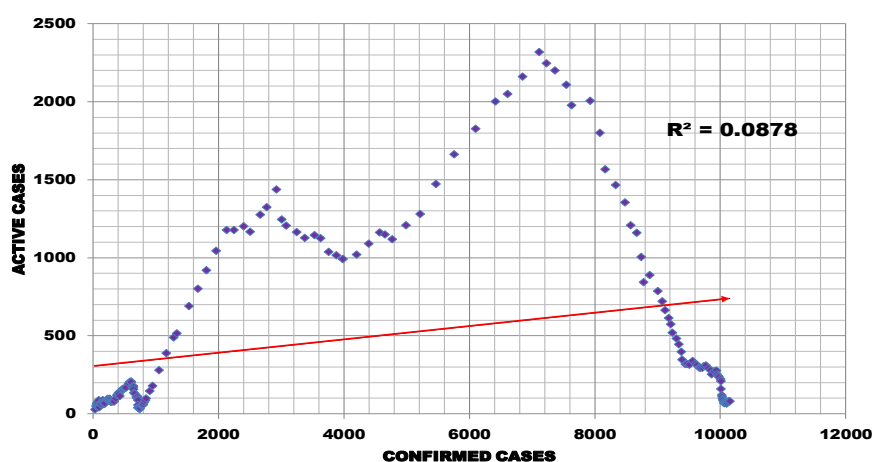


FIGURE-4

Figure 4: There was no correlation between total number of confirmed cases of covid-19 and number of active cases of COVID-19.

However, though there was no mortality from COVID-19 for a prolonged period of time in the population after the onset of COVID-19, there was an abrupt increase in mortality rate from the beginning of the second wave. The increase in mortality rate could be due to higher viral load which was lethal for survival, irrespective of the immune status of affected individuals. The Figure 5 also reflected that though the mortality rate from COVID-19 abruptly increased, the number stabilized

after some time and remained so until 31 July 2021. However, due to steep increase in mortality for a brief period of time, the trend line showed a significant value with $p \leq 0.01$.

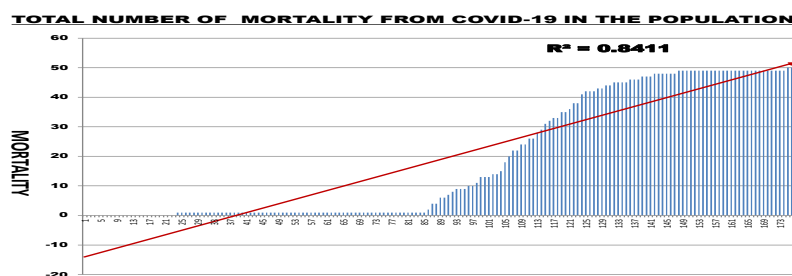


FIGURE-5

Figure 5: A significant increase in overall mortality from covid-19 in the population was observed.

However, the correlation study between the overall mortality in the population during the entire period of six months and the total number of active cases, showed a non-significant value. The result is depicted in Figure: 6.

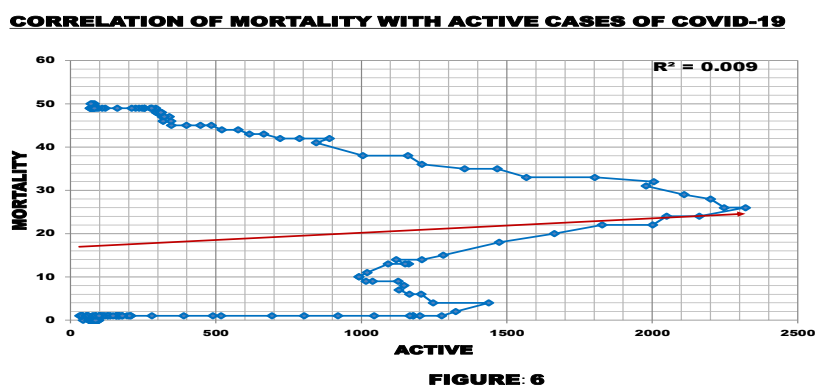


FIGURE: 6

Figure 6: No correlation was noted between the number of mortality from COVID-19 and active cases of COVID-19 when evaluated for the entire period.

In this study, there was high and significant increase in the number of recovered cases from COVID-19 (98.7%), and a correlation study between the two variables was highly significant ($p \leq 0.001$) as shown in Figure: 7. Another interesting fact noted from the recovery study was that the trend line and the actual number of recovered cases were overlapping from the time COVID-19 appeared in the population in January, 2021 until 31 July, 2021. This outcome suggested that a persistent resistance to SARS-CoV-2 infection existed in the population. The data was highly significant with $p \leq 0.001$.

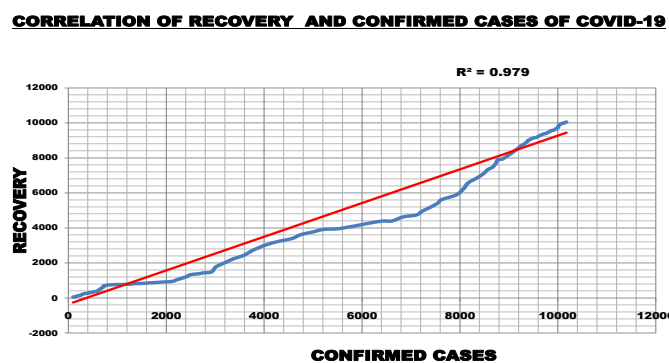


FIGURE: 7

Figure 7: The graph depict a positive correlation between trend of recovered and total number of COVID-19 cases ($p \leq 0.001$).

The high number of recovered cases concomitant with lower number of active cases was reflected in the rate of ‘doubling’ time of COVID-19 in the population. The data is shown in Figure: 8. It is clear from the graph that the doubling time of COVID-19 was five days which gradually increased reaching a peak of 37 days and subsequently decreased to 7 days, during the second wave, and then the doubling time showed an upward trend reaching to 22 days by 1st June, 2021 and continued falling until July 31, 2021. The doubling time of COVID-19 was consistent with the ‘two waves’ that was observed with the number of active cases as shown in Figure: 3 and a flattened growth curve of COVID-19, as shown in Figure: 1.

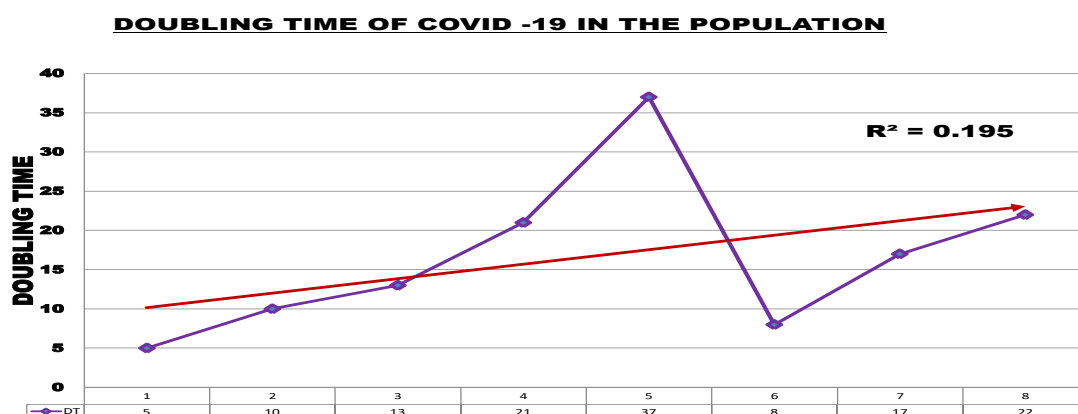


FIGURE:8

Figure 8: The graph depict the doubling time of COVID-19 in the population which registered a gradual increase in doubling time.

One major conclusion that could plausibly be drawn from the entire study was the rise and rapid wane of active cases of COVID-19 in the population. This rapid fall in number of active cases was plausibly due to the presence of prior immunization in the population. The mass vaccination program with MMR vaccine undertaken in 2017 in the entire population played a significant role in development of immunity against SARS-CoV-2. It was previously articulated that the Lakshadweep population being immunized against Mumps, Measles & Rubella earlier, was an impediment for the spread of SARS-CoV-2 in the population^[8]. And the infectivity rate of the virus during the early stage of the pandemic was very low and individuals with lower load of the virus showed a mild form of COVID-19 from which most of the individuals were able to recover completely.

As stated in the above paragraphs that the population of Lakshadweep had a prior history of immunization. And under the Measles-Rubella (MR) campaign undertaken by the Government of India in collaboration with World Health Organization (WHO) in 2017, all children in the target age group (between 9 months and less than 15 years) were given a single shot of MR vaccination, irrespective of their previous measles/rubella vaccination status or measles/rubella disease status, to boost the immunity and protect the entire community against transmission of measles and rubella. A Study reported by Gold *et al* showed that antibody against MMR vaccine was found in individuals who recovered from COVID-19 suggesting that the memory cells to MMR vaccine actively

participated in neutralising the SARS-CoV-2 virus. The significance of that study lay in the fact that mumps titers related to the vaccine were significantly and inversely correlated with the severity of COVID-19-related symptoms, supporting the theorized association between the vaccine and COVID-

Analysis of MMR Titers of Recovered COVID-19 Patients

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Mumps Titer vs. COVID-19 Severity (MMR II Group, n=50)

$r_s = -0.71, P < .001$

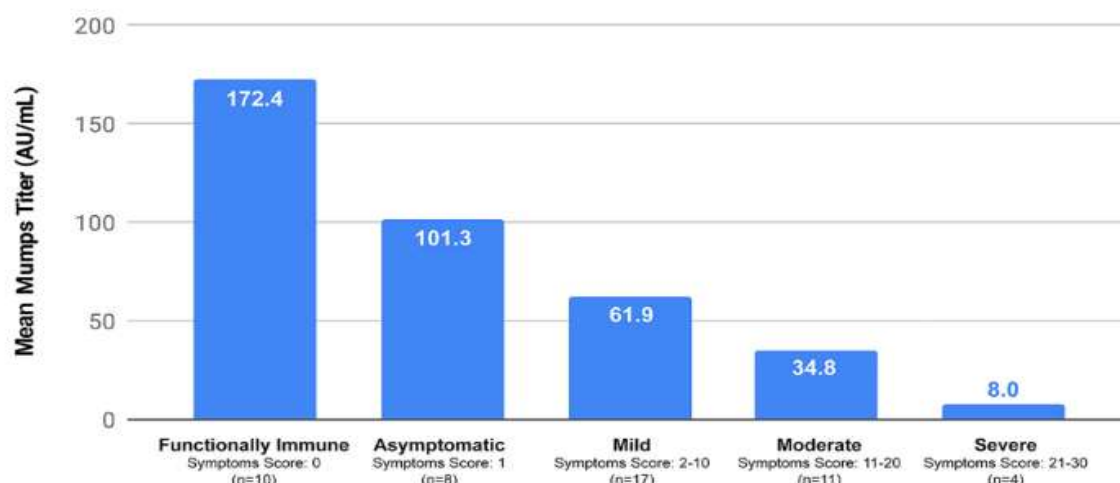


FIG 1 Mean mumps titer values (in arbitrary units per milliliter) were compared to each of five severity categories. Each severity category was based upon the symptom scores shown in Fig. 2. "Functionally Immune" data represent subjects with a severity score of 0. "Asymptomatic" data represent those with a score of 1, i.e., those who were COVID-19 positive but had no symptoms. "Mild" data represent those with scores ranging from 2 to 10. "Moderate" data represent those with scores ranging from 11 to 20. "Severe" data represent those with scores from 21 to 30. A P

Figure 9: Analysis of MMR titers after recovery from COVID-19 (reference-9)

19 severity (9). A significant inverse correlation between mumps virus titers and COVID-19 severity within the MMR II group was observed in that study (Figure: 9). A survey of presence of MMR antibody in the recovered COVID-19 individuals in Lakshadweep is being planned to be undertaken. As pointed out earlier in our report^[8] that ours was the first field observation which had corroborated with the finding in the MMR study theorizing association between MMR vaccine and COVID-19 severity.

Similar studies which investigated the effectiveness of booster vaccination of adults with measles-mumps-rubella in the COVID-19 infection rates predicted that immunity produced by MMR vaccination boosters could provide some degree of protection against COVID-19 in the adult population and it could help develop immunological memory^[10,11]. Corroborating this observation, scientific studies have shown that immune cells which were exposed to a viral antigen responded to related/unrelated viral antigen(s). It was observed in a study that blood collected from SARS-CoV-1 infected individuals in the year 2015, mounted an immune response, *in vitro*, against SARS-CoV-2 infected cells in 2020, without being exposed to the SARS-CoV-2 virus. This suggested that immunological response generated in the SARS-CoV-1 infected individuals could cross-act against SARS-CoV-2 virus; probably because both the virus were having similar backbone DNA^[12].

Analysis of immunological and epidemiological data on endemic human coronavirus (HCoV) showed that infection-blocking immunity wanes rapidly, but disease-reducing immunity was long-lived^[13]. This was also evident from the data presented in this study. However, with the appearance of delta-variants of SARS-CoV-2 due to selection pressure, vaccination, in addition to having immunity against the virus, is the only effective way to fight the fast changing SARS-CoV-2 virus.

Unfortunately, the vaccines available until now have shown to generate predominantly a B- cell response. Whereas, effective vaccine against a virus requires to engage both cytotoxic and helper T cells, as the figure given below demonstrate (Figure: 10).

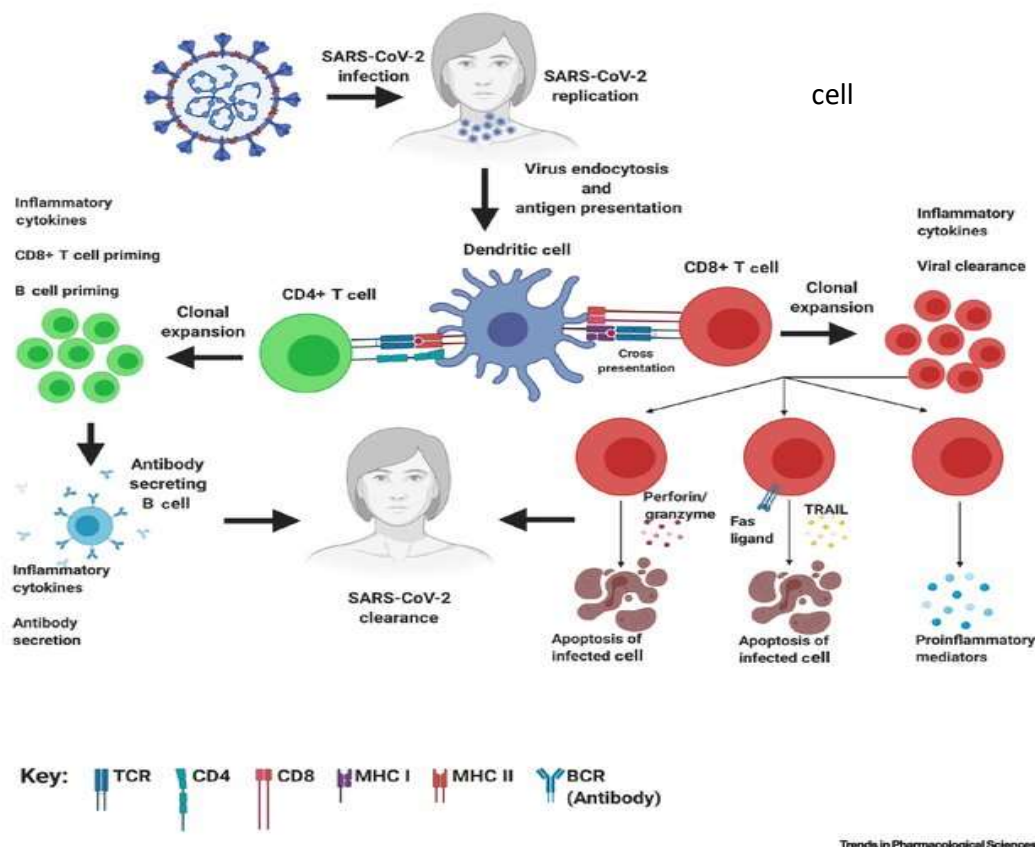


Figure: 10

It is apparent that for ending the current COVID-19 pandemic and to prevent recurrence of the disease requires the development of vaccines that provide long-lasting immunity to the causative virus, the SARS-CoV-2, and to achieve this, a vaccine must elicit both CD4+ and CD8+ T cell immunity in addition to the production of neutralizing antibodies (nAB) by B cells. The rationale is based on the findings for SARS-CoV-2 and the related SARS-CoV virus which caused the 2002/2003 SARS pandemic that there is important need to design COVID-19 vaccines which co-engage T cells in addition to B cells for generating long lasting memory^[14,15].

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