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Increased Doubling Time with Significant Recovery and Low Mortality from COVID-19 following Extended Lockdown: Implication for Development of Protective Immunity against SARS-CoV-2 in a Population

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Abstract

BACKGROUND: COVID-19 is fast spreading around the globe in a highly contagious manner. Until date there are no therapeutic agents/vaccines developed which could control this highly infectious virus from spreading among human population. At this juncture, therefore, controlling the spread of this highly contagious disease is a priority which could be only achieved by implementing stringent Lockdown and maintaining Social Distancing. Our earlier findings in Indian Population, in this direction, reflect that early introduction of complete Lockdown significantly controlled the spread of COVID-19 in the population.

METHODS: The methods undertaken for this study was collection of data from established sources, about COVID-19 pandemic. Evaluation of the data was done by statistical analysis (Microsoft Excel & power point, Pearson Correlation Coefficient etc.)

RESULS: The results from our study showed that after intervention with successive Lockdowns, there was marked decrease in the rate of COVID-19 cases, though there was sporadic volatility in number of COVID-19 cases due to some extrinsic factors. Concomitant with reduction in rate of COVID-19 there was gradual increase in doubling time of COVID-19, steady increase in number of discharged/recovered patients from COVID-19 reaching to a level of ≥ 58%; taking the entire Indian population into consideration. Another important aspect was consistent low mortality rate that was associated with gradual increase in the rate of recovery from COVID-19 in the population.

CONCLUSIONS: In conclusion it was established from this study that implementation of contentious & prolonged Lockdown was able to slowdown the rate of spread of COVID-19 among the entire population. The increased doubling time of COVID-19, low mortality and high recovery rate following the intervention plausibly points to the development of protective immunity in the population.

Key words: COVID-19 – interventions- growth curve- recovery – mortality -protective immunity.

Background

The novel coronavirus (SARS- COV-2) originated in Wuhan in Hubei province of China during December 2019, and has now spread across the Globe making it a pandemic. Until date there are no therapeutic agents/vaccines developed which could be of promise to control this highly infectious virus from spreading among human population. At this juncture, therefore, controlling the spread of this highly contagious disease is a priority.

SARS virus belongs to the family Coronaviridae, which is known to cause respiratory illnesses in humans and animals. coronavirus (CoV) is a novel member of this family that causes acute respiratory distress syndrome (ARDS), which is associated with high mortality rate. Its characteristic feature is long latency period before a typical flu-like fever, cough, and shortness of breath manifests. The people infected with this virus may not show any early symptoms allowing them to pass it on to others unknowingly.

Due to alarming nature of this disaster world-wide and to contain its spread at an early stage, a short curfew followed by 'National Lockdown' for 21 days starting from 23rd March, 2020 Midnight until Midnight of 14 April, 2020 was implemented by Indian Authorities. Following which the Lockdown was extended twice ultimately ending on 31 May 2020 (Lockdown-4). We have described earlier a method to monitor the spread of COVID-19 among the population during Lockdown-1 and showed that during this period number of COVID-19 cases abruptly came down and

maintained a flattened curve until 31 March, 2020. However, there was some volatility due to spurt in the number of cases on 1st April, 2020 onwards due to some extrinsic factors. At this stage, Lockdown was further extended for two weeks from 14th April until 30 April, 2020 (Lockdown-2), until 17 May 2020 (Lockdown-3) and until 31 May, 2020 (Lockdown-4) respectively.

In this article, we have endeavoured to elucidate the role of prolonged Lockdowns on the spread and control of COVID-19 and possible significance of the changes on development of protective immunity within the population.

Methods: The present study was carried out on the data collected from different sources that include the Ministry of Health (Health bulletin) Government of India and from other National and International News outlets starting from March 15, 2020 until March 25, June, 2020 as also described previously by us (1, 2, 3). The Statistical analysis was performed by Microsoft Excel and power point programs and the correlation studies were done using Pearson Correlation Coefficient program.

Results: The Figure 1 reflects the total number of reported cases of COVID-19/day until the end of Lockdown-4, that is 31 May, 2020. The graph reflects that there was a gradual increase in the number of COVID-19 cases since 15 March, 2020 until 31 May, 2020. However, the trend line shows that the actual number of

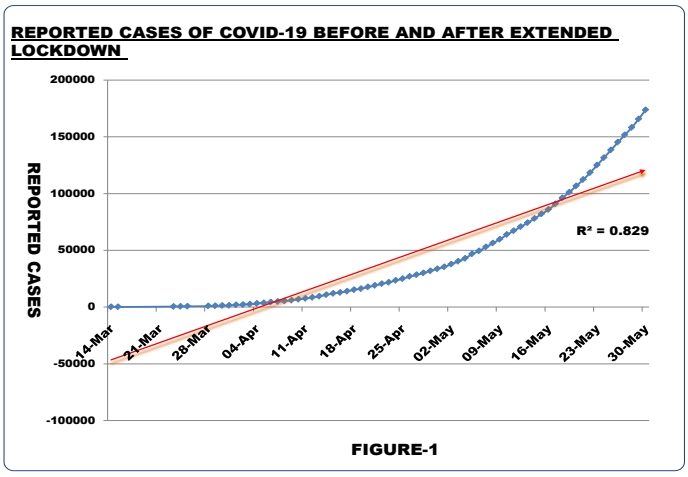

Figure1: The graph depicts the total number of COVID-19 positive individuals in Indian Population at different time points between 15 March, 2020 and 31 May, 2020 (end of Lockdown-4). As evident from the graph, there is an increase in number of positive cases in the population before and after four Lockdowns spanning 68 days.

COVID-19 cases could have been much lower than the reported number which plausibly was due to sudden spurt in number of cases, once immediately after lockdown-1 from single source and the second spurt in the number of COVID-19 cases was due to unprecedented movement of ~ 6.3 million migrant labourers across the country during Lockdown-3 & 4 (R2 = 0.829). These changes in the rate of COVID-19 are reflected in Figure-2. It shows that after Lockdown-1 was implemented on 25th March 2020, there was marked decrease in the rate of COVID-19 cases in the population, which was stably maintained until 31 March 2020. However, on the 1st of April, 2020 a spurt was noted in the COVID-19 cases and there was 2.5 folds increase in COVID-19 cases compared to 31 March, 2020. This abrupt change in number of COVID-19 cases was due to contribution of cases from a 'single source' (2). Later contribution from a 'second source' representing

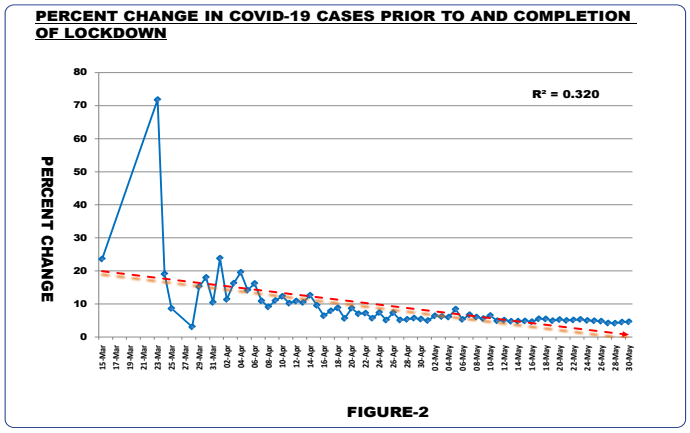

Figure 2: The graph shows the percent change in COVID-19 cases from15 March, 2020 until 31 May, 2020 (end of Lockdown-4). The graph reflects that following implementation of four 'Lockdowns', a flattened growth curve was maintained from around 15 May, 2020. However, the trend line shows that the number should have been much lower at the end of lockdown-4.

migrant labourers caused abrupt increase in number of COVID-19 cases. All such spurts appeared as small peaks in the percent graph. As reflected in the graph, around 14th May, 2020, the rate of COVID-19 cases stabilised at ≤ 4% which was maintained until the end of Lock-down 4. However, the trend line suggests that by the end of Lockdown-4, the rate of COVID-19 case should have been much lower than the actual value recorded in the graph (R 2 = 0.320). The trend line also confirmed that the 'spurts' had a negative impact in the rate of spread of COVID-19 cases among the population. The Figure-3 gives a comparative rate of COVID-19 during Lockdown-3 and Lockdown-4 respectively. The comparative study shows that the volatility in rate of COVID-19 cases had decreased during the period of Lockdown-4 with R 2

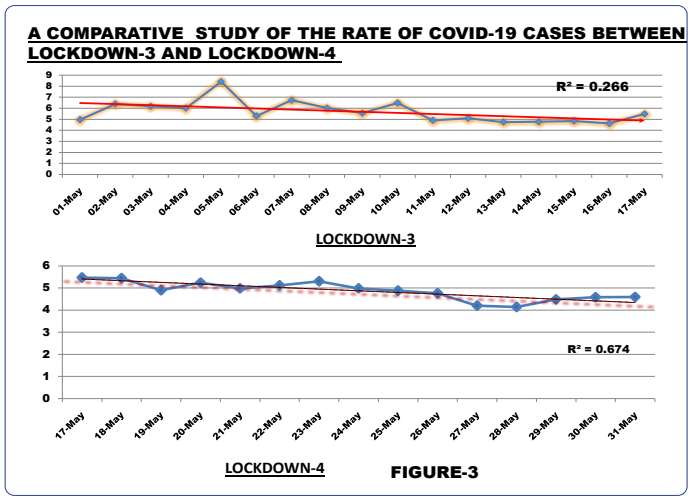

Figure 3: The Figure shows a comparative representation of the rate of COVID-19 during lockdown-3 and lockdown-4 respectively. The comparative graph reflects that the volatility seen during earlier Lockdowns was reduced and stabilised during lockdown-4 and the rate of reported cases of COVID-19 was ≤ 4.6%.

value being = 0.674, and the value of R 2 being = 0.266 during Lockdown-3. It is also clear from the graph that the actual rate of growth of COVID-19 came down from 5% to ≤ 4.5 % by the end of Lockdown-4 on 31 May, 2020. Interestingly, with noticeable stability achieved in rate of COVID-19 cases by the end of Lockdown-4, the number of patients recovering from COVID-19 also increased steadily. The Figure: 4 shows that the percent of recovered patients were consistently high compared to reported cases, at the end of Lockdown-4 and subsequently the percentage gradually increased which is demonstrated in

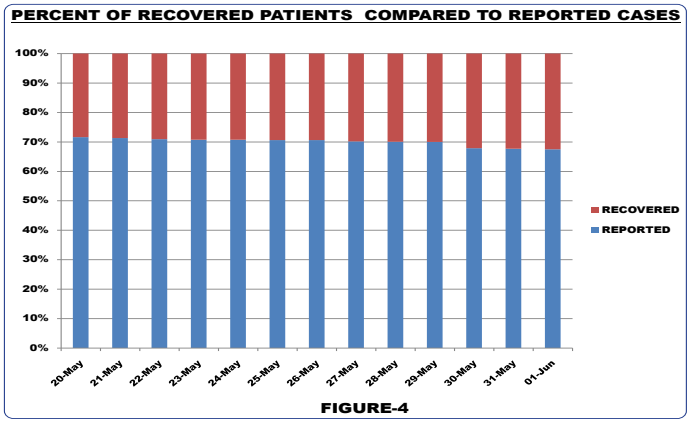

Figure 4: The graph shows that the number of recovered cases of COVID-19 compared to reported cases during lockdown-4. The number of recovered individuals gradually increased to more than 30% in the graph. Later, as of 29 June 2020, nearly 60% patients suffering from COVID-19 recovered.

Doughnut chart (Figure 5). A Doughnut chart meant to express a "part-to-whole" relationship, where all pieces together represent 100%, shows the recovery rate on 01 June, 2020 (immediately after lockdown-4) and later on 15 June 2020. It is clear from the chart that the recovery rate was 48% on 01 June, 2020 and 54% on 15 June, 2020 as compared to total confirmed cases. Interestingly, the number of recovered individuals was approximately equal to the number of active cases of COVID-19 after lockdown-4. Due to significant recovery from COVID-19 cases, it was of interest

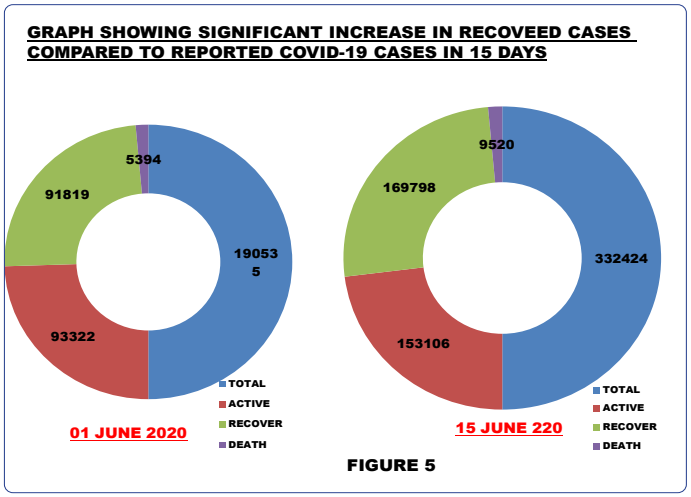

Figure 5: The doughnut charts show the distribution of Total, active, recovered and deceased individuals with COVID-19 on 1 June, 2020 and 15 June, 2020.

to see if any correlation existed between rate of recovery and rate of COVID-19 cases. The Figure-6 reflects that there was a weak negative correlation between the two variables with R 2 = 0.296.

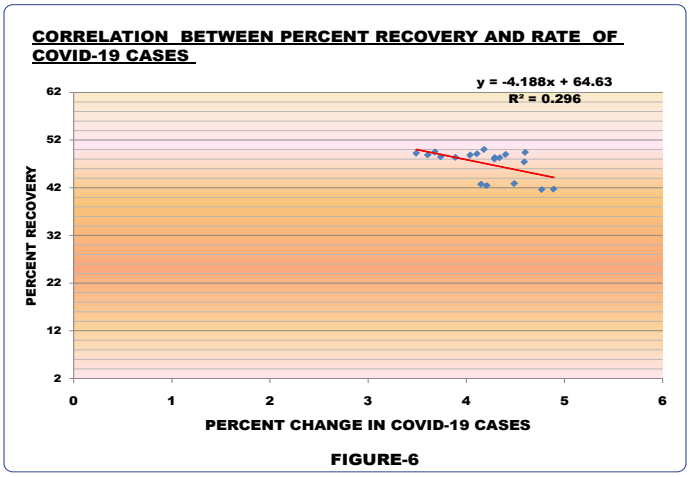

Figure 6: The Figure shows the correlation between percent of recovered individuals from COVID 19 and the rate of COVID-19 cases. As reflected in the graph weak negative correlation existed between the two variables.

Another noteworthy aspect of the study was that with gradual increase in recovery rate, the mortality rate was consistently very low as shown in Figure-7. The mortality rate has been consistently maintained at ~2.8% from the beginning, whereas the recovery rate continues to rise and presently it is ~60%. When a correlation was drawn between the mortality rate and the rate of COVID-19 cases a weak negative correlation between the two variables with

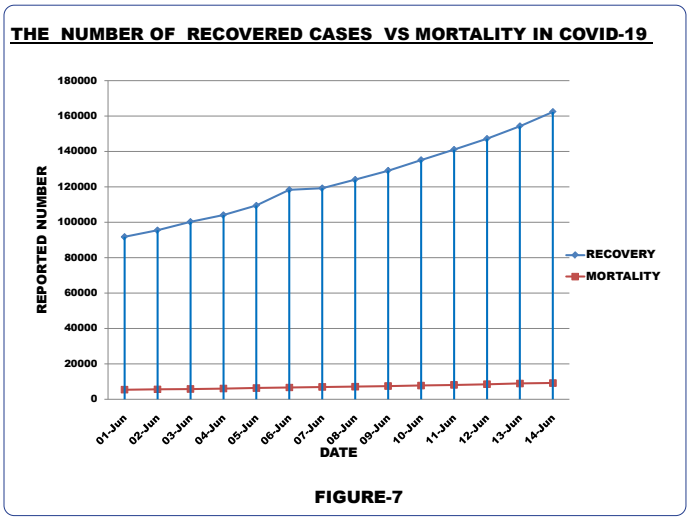

Figure 7: The Figure shows the number of recovered individuals and mortality from COVID-19 between 1 June, 2020 and 14 June, 2020. It is clear from the Figure that while the mortality was consistently same, the number of recovered individuals steadily increased during the same period.

R 2 = 0.21 was observed as shown in Figure-8. With gradual decrease in the rate of COVID-19 cases to below ~4% at the end of lockdown-4, the doubling time of the COVID-19 cases also increased to 15 days as on 5 June 2020. When the two variables were plotted on correlation coefficient graph, a weak negative

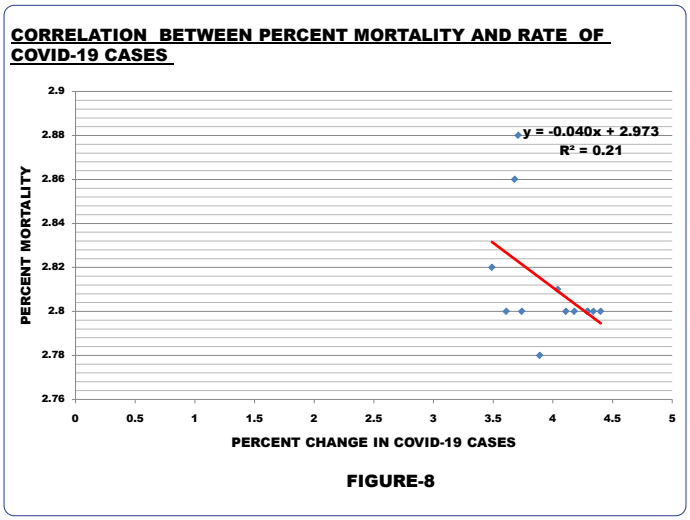

Figure 8: The Figure shows correlation between mortality rate and rate of COVID-19 cases. A weak negative correlation between the two variables with R 2 = 0.21 was observed.

correlation was noted with R2 = .082, as shown in Figure-9. The results discussed so far, suggests that gradual increase in the number of Recovered/disease free individuals with time to above 50% along with a negative correlation between the doubling time and the rate of reported COVID-19 cases implies that the

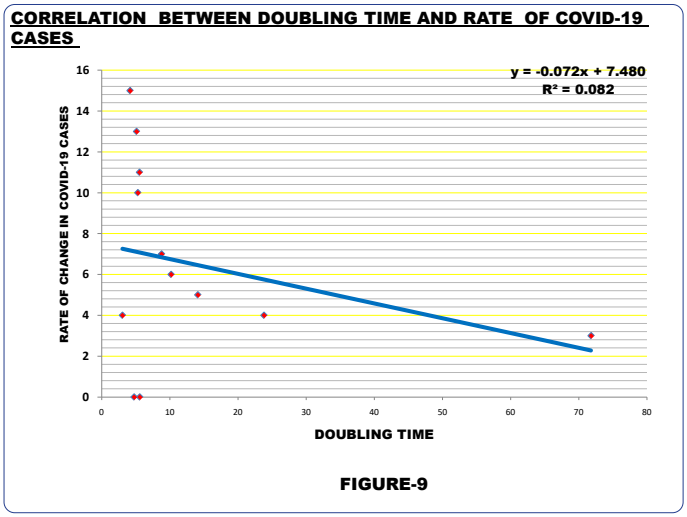

Figure 9: The Figure shows the correlation between the doubling time of COVID-19 cases and rate of COVID-19. A weak negative correlation was noted between the two variables with R2 = .082.

Indian population could be steadily moving towards developing protective immunity against COVID-19. The Figure-10 shows the distribution of COVID-19 cases in some states of India with high number of COVID-19 cases compared to rest of India. The Figure emphasizes that a few states have the bulk of COVID-19 cases compared to rest of the country.

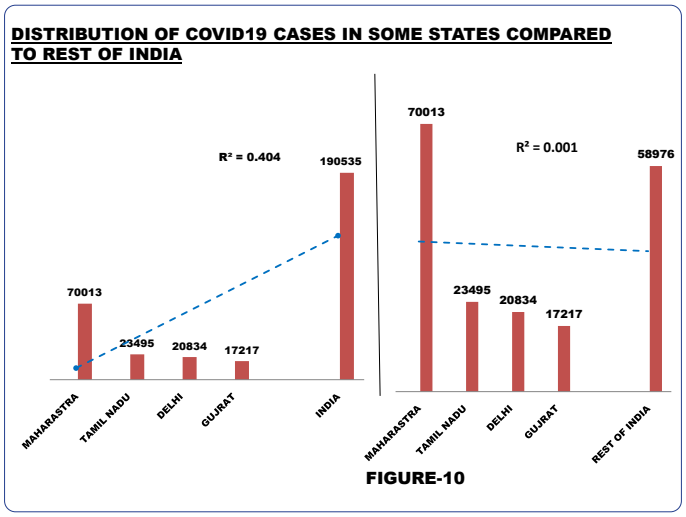

Figure10: The graph shows the distribution of COVID-19 cases in some states of Indian union as compared to rest of India. The point to note in the graph is that the state of Maharastra alone has more cases of COVID-19 than the rest of India (excluding Tamil Nadu, Delhi & Gujarat).

Conclusions:

The disaster caused all over the world due to COVID-19 pandemic has prompted a massive global effort to control its spread in their respective population. At present, due to lack of any specific treatment regimen for COVID-19, the importance of implementing Lockdown/social distancing at an appropriate time cannot be ignored at all. Delaying implementation of specific intervention/social distancing in the USA by only few weeks resulted in heavy loss of human lives as depicted in the model shown in Figure-11.

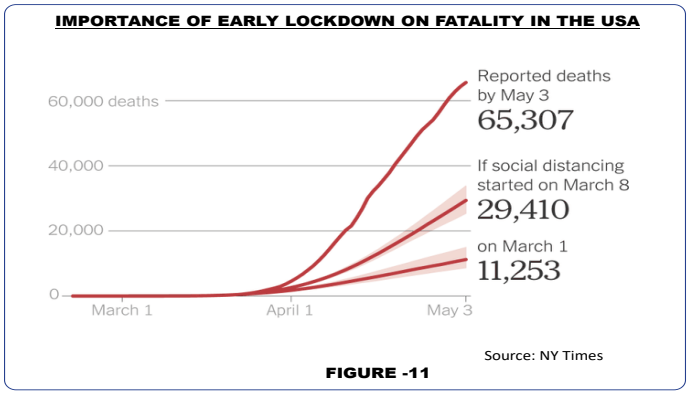

Figure 11: The Figure is to show the positive effect of intervention by lockdown/social distancing. It is clear from the graph that there was six times increase in fatalities for delayed implementation of social distancing in the USA (The graph has been taken from NY times, USA).

India however, by introducing physical intervention with social distancing rather early on March 23, 2020, when number of COVID-19 positive cases was negligible, achieved rapid arrest of COVID-19 cases among Indian population as reported earlier by us (1). Though there was substantial volatility in the rate of COVID-19 during Lockdown-1, it gradually subsided by the end of Lockdown-4. Such alteration in volatility during successive Lockdowns was reflected from the improved R2 value at the end of Lockdown-4. The reduced volatility and sustained flattened

curve at a fixed rate of COVID-19 at the end of Lockdown-4, along with increased doubling time of COVID-19 to 15 days on 5 June, 2020 conclusively demonstrated that spread of COVID-19 was gradually slowing down in the population. Additionally, steady increase in number of discharged/recovered patients from COVID-19 with sustained lower rate of mortality also points to the gradual waning of the SARS-CoV-2 virus.

Immunity and COVID-19: It has been observed that the recovered patients across the world showed presence of antibodies against the novel coronavirus, SARS-CoV-2, and transfer of 'Plasma' taken from such recovered patients were able to cure patients suffering from COVID-19. Studies from South Korea and other countries have confirmed that an immune response develops in recovered patients. In a study in the USA, it was demonstrated that specific T cells could have played a role in fighting the disease at later stage of infection with SARS-CoV-2. A recent preprint has corroborated that divergent SARS-CoV-2-specific T and B cell responses were seen in severe but not mild COVID-19 (4). All such studies have repeatedly demonstrated that a long term memory T-cell mediated response is vital for eradicating the viral infection. Therefore, it is reasonable to speculate that an earlier presence/induction of specific T cell response against the SARS-CoV-2 may become a game changer for the treatment of COVID-19.

A case of protective Immunity: Given the importance of immunity in natural control of any viral disease including COVID-19, it is worthwhile to develop means for pan-protection of a population against SARS-CoV-2. The important point of recognition in the present study, towards that direction, is existence of negative correlation among the vital parameters of recovery, doubling time and rate of COVID-19 cases; such finding would plausibly suggest that there is a gradual development of protective immunity within the population.

Protective immunity/Herd immunity, also called herd protection, is the resistance to the spread of a contagious disease within a population that results if a sufficiently high proportion of individuals become immune to the disease. It basically serves as an indirect protection to those who are not immune to the disease. This type of protection could also be achieved either through vaccination or from exposure to previous infections. Analysis of the data available from different parts of the world suggests that when the corona virus, SARS-CoV-2, did not meet any substantial resistance (immune response) in a population, it was able to spread quickly and subsequently cause havoc in a population. In India however, the picture appears to be apparently different for various reasons/factors. Firstly, in Indian population, the novel coronavirus met with stringent resistance by way of physical intervention & social distancing at an early stage, which not only disallowed its spread far and wide but also broke its chain of movement locally. This abrupt slow down in the mobility of the virus, as reflected in the lower rate of COVID-19 (Figure: 2), resulted in gradual weakening (attenuation) of the virus and aided in development of 'natural immunization'. Secondly, abrupt spurt in the number of COVID-19 cases on two occasions; once on 1st April, 2020 from a 'single source' as described earlier (2, 3) and on 1st May, 2020 onwards, due to mobility of large number of migrant labourers (~6.3 million) returning to their respective home states, in trains, buses & by foot from across India during Lockdown-3/Lockdown-4, without maintenance of 'social distancing', should have derailed the effect of Lockdown on rate of COVID-19 cases. However, the silver lining is that such unprecedented event did not spell disaster until now. This outcome could be attributed to the fact that majority of such migrant individuals may have had prior immunization/exposure to related/unrelated infectious agents that protected them against the infection of SARS-CoV-2. Immunologically, this could be due to presence of cross reacting T cells already present in most individuals as a result of prior infection or passive immunization to a related agents. The Table-1 lists the different vaccines used in India since 1893 (5), which could have aided in developing this type of immune response. A recent article published in the journal Cell has precisely demonstrated that blood samples collected from a group of 20 people in 2015, who were never exposed to the novel coronavirus, SARS-CoV-2, had cross-reactive Th cells that were capable of recognizing & responding faster to the novel coronavirus, SARS-CoV-2 (Figure-12; Reference: 6). In Indian context, a large number of people in the population have been previously immunized against many of the deadly microbe borne diseases like TB, small pox, diphtheria etc (as shown in Table-1),

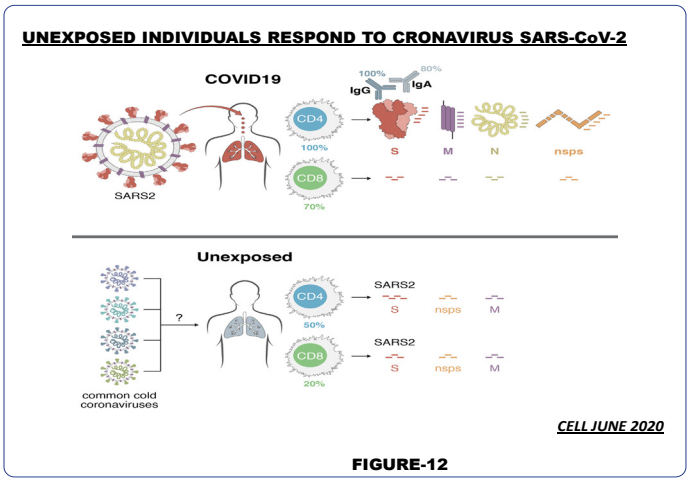

Figure 12: The Figure is an illustration which reflects that the persons who were never exposed to the novel coronavirus, SARS-CoV-2, had cross-reactive Th cells that were capable of recognizing & responding faster to the novel coronavirus, SARS-CoV-2 (Reference: 5).

either by vaccination during childhood or by getting cured from the disease itself (5). In a recent study in the USA, BCG vaccine which is used for vaccinating against TB, when used to vaccinate a large number of individuals in American Indian population prone to lung cancer, has shown to reduce the risk for developing lung cancer in a clinical trial conducted in American–Indian and Alaska Native populations (7).

Though in classical scenario of herd protection, it requires significant percentage of people to be immune against the virus in a population, however, in case of Indian population diverse cross reacting memory T-cells may already be present to respond actively against the SARS-CoV-2 virus and its attenuation due to successful and prolonged Lockdown may, additionally, facilitated passive immunization to those who were not previously immunized with a related agents. In an unrelated study, we have previously shown that it was possible to generate a long term T cell response by attenuating tumour cells in vivo by irradiation (8).

Results from this study, do reflect that there are early signs of development of protective immunity against the novel coronavirus in the population.

Though it is presently believed that as long as there are susceptible and infected people in the population, the virus could spread, data accumulated during the last three months reflect that first wave

HISTORY OF VACCINATION IN INDIA

Year	Milestone
1893	Efficacy trials on cholera vaccine conducted in Agra, India
1897	First plague vaccine discovered by Dr Haffkine
1904/1905	First vaccine research institute established at Kasauli, Himachal Pradesh
1907	Pasteur Institute of India, Coonoor, manufactured neural tissue anti-rabies vaccine
1920-1939	DPT, DT and TT vaccine became available in the country
1940	Drug and Cosmetics Act enacted
1948	BCG vaccine laboratory set up in Guindy, near Madras (Chennai)
1951	Liquid BCG vaccine became available in India as part of mass campaigns
1965	Live attenuated freeze dried smallpox vaccine became available
1967	Freeze dried BCG vaccine became available OPV became available in India
1970	The first time in India indigenous Oral Polio Vaccine Trivalent (Sabin) was developed and produced
1980s	Indigenous measles vaccine production started
1984	Inactivated polio vaccine first produced in India (later on production stopped)
1985/1988	AEFI surveillance system established and initial guidelines were released
1989	Indian Vaccine Company Limited (IVCOL) and Bharat Immunological and Biological Limited (BIBCOL) were set up as public private joint venture companies
1997	First ever recombinant DNA hepatitis B vaccine developed in India
2006	Guidelines for clinical trials by Indian Council of Medical Research (ICMR)
2009	Three Indian manufacturers developed pandemic flu (Novel H1N1: 2009) vaccine
2010	National Pharmacovigilance Programme of India launched Meningitis A vaccine for African Meningitis Belt licensed and successfully used in campaigns in Africa Indigenously researched bivalent oral cholera vaccine developed and licensed in the country
2012	An indigenous 'inactivated JE vaccine' licensed in the country. Indian manufacturer acquired capacity to produce inactivated polio vaccine

Source : Refs 4, 6, 27-30
DPT, Diphtheria, pertussis and tetanus; DT, diphtheria and tetanus; TT, tetanus toxid; OPV, oral polio vaccine

TABLE-1

Table 1: The table lists the different vaccines used in India since 1893. The population immunized/cured from any of the vaccines/disease have a plausible chance to respond to the novel coronavirus, SARS-CoV-2 (reference: 6).

of the epidemic has been substantially controlled as a result of prolonged Lockdown and for presence of immunity to fight the virus in the population. Another aspect to be considered seriously is that for the success of development of immune protection in the entire population, sustained Lockdown and maintaining social distancing norms is mandatory for gradual 'attenuation' of the virus.

Abbreviations: Not applicable

Declarations:

1. Ethics approval and consent to participate: Not Applicable
2. Consent to publish: Yes
3. Availability of data and materials: From public domain (Ref: 1, 2, & 3).
4. Competing interests: No competing interest
5. Funding: No funding was available for this study
6. Authors' Contributions: Full
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