

Available online on 15 Mar, 2021 at <https://ijdra.com/index.php/journal>**International Journal of Drug Regulatory Affairs**Published by Diva Enterprises Pvt. Ltd., New Delhi
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Review Article

COVID-19, Herd Immunity and Nanotechnology- A ReviewRavi Kumar Sah^{*a}, Mukesh Kumar Bhagat^a, Upama Niraula^b^aAcharya and B M Reddy College of Pharmacy, Bangalore, India- 560107^bNepalese Army Institute of Health Sciences- College of Nursing, Kathmandu, Nepal**Abstract**

Covid-19 had been the global pandemic cases across the world since WHO declared it as pandemic diseases. It has been global crisis which had impacted globally on health and economic sector at a time. This review article had covered the detail of COVID-19 in brief detail, its epidemiological data, herd immunity and vaccination program, vaccine development status. Also this article the nanotechnology used in vaccine development process and its future prospective. This article had been concerned over the SAARC Nations epidemiology data related to COVID-19.

Keywords: SAARC, Vaccination, India, Global Pandemic**Article Info:** Received 07 Jan. 2021; Review Completed 26 Feb. 2021; Accepted 28 Feb. 2021**Cite this article as:**Sah RK, Bhagat MK, Niraula U. COVID-19, Herd Immunity and Nanotechnology- A Review. Int J Drug Reg Affairs [Internet]. 2021 Mar 15 [cited 2021 Mar 15]; 9(1):15-21. Available from: <http://ijdra.com/index.php/journal/article/view/451>

DOI: 10.22270/ijdra.v9i1.451

*Corresponding author

1. Introduction

The novel coronavirus i.e. the COVID-19 cases got outbreak from the city Wuhan of the China at mid December 2019 whereas the first cases of COVID-19 had been traced backed in 17th November 2019. (1) Earlier to this COVID-19, 2 more cases of the coronavirus outbreak had happened. The first outbreak was known as Severe Acute Respiratory Syndrome (SARS) which got outbreak in 2002 and second case of outbreak mainly known as the Middle East Respiratory Syndrome (MERS) came in 2012. From the data analysis of the all these three cases of coronavirus outbreak, the SARS and MERS had been found to have the higher mortality rate in comparison to the COVID-19. (2,3)

The COVID-19 had been firstly considered as the Public Health Emergency and International Concern and was declared so by WHO on 30th January 2020. (4) Soon later, it got emerged as the Global Crisis as it got spread out from the Mainland of China to other parts of the world. The number of cases in the other countries increased more than that in the mainland of China. Thus the WHO declared the COVID-19 as Pandemic Diseases on the 11th March 2020. (5)

The actual and 100% effective treatment had not been developed till date (2nd August 2020). The treatment of COVID-19 now is based on the drug repurposing strategy of the pre-approved medications for other

diseases treatment which had been considered as Safe for Human use after clinical trials. (6)

For the treatment as well as the prevention of the population from getting infected from the COVID-19, there is emergency need of a novel vaccine against the COVID-19 coronavirus. There had been more than 150 vaccines in the process of development and among them the 29 vaccines is been already in different *clinical* trial stages at present. But none of the vaccines has completed its complete clinical trial so as to be called Safe for Human use. (7)

For providing the immunity against the COVID-19 coronavirus, the Herd immunity concept had been taken into consideration and the different studied had been carried out on Herd immunity.

This review article has covered the COVID-19 cases, the Herd immunity and nanotechnology prospective related to it.

2. Description

COVID-19 is the infectious disease which is caused by the novel coronavirus. This virus most probably attacked the host respiratory system which causes the mild to severe respiratory problem. COVID-19 is characterized by the sign and symptom like cold, fever, nasal congestion, fatigue, etc. (8)

The word coronavirus is derived from the Latin word based on the surface structure of the virus. In Latin corona means the crown. As the structure morphology of COVID-19 is spherical virions with a core shell. Also on the surface, there is projection of spike like structure which resemble to the solar corona. Thus the name of virus is the coronavirus. (9,10)

Coronavirus are positive single stranded large RNA virus approximately of 26-32 kilobases in size which affects the human as well as the larger species of animals like camel, bat, pig, etc. Coronavirus is categorized into 4 subfamilies. These families are known as the a) Alpha-, b) Beta-, c) Gamma-, and d) Delta. The alpha and beta are originated from the mammal like bats whereas the gamma and delta are originated from the pigs and birds. From the study it has been found that, alpha and beta subfamilies virus causes the infection to human mostly. The infection caused by the alpha coronavirus is mild

symptomatic infection or the asymptomatic. But the infection caused by is the server form of the infection which leads to death also.

The present COVID-19 causative coronavirus belongs to the beta subfamily of coronavirus and at whole genome level it is 96% identical to a bat originated coronavirus. These beat coronavirus consist of four structural gene. These gene are nucleocapsid protein (N), spike protein (S), small membrane protein (SM) and membrane glycoprotein (M). The study report had showed the possible animal to human and human to human transmission via nasal droplets and direct contact. The prevention for the COVID-19 pandemic via break down of transmission process from human to human by maintaining social distance by following WHO safety Guideline for COVID-19 pandemic and by mass vaccination to develop the herd immunity against COVID-19 infection. (11,12)



Figure 1. Process of transmission of COVID-19 infection

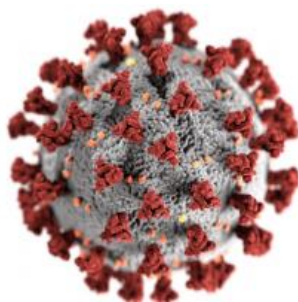


Figure 2. Coronavirus (13)

3. Epidemiological characteristics of COVID-19

The novel COVID-19 has infected 215 countries, territory or conveyance all over the world as pandemic disease case. The total number of confirmed cases all over the world till date is been found to be 20,021,321. Among these confirmed cases, 12,896,895 cases has recovered from COVID-19 after treatment and 733,918 persons died due to COVID-19 out of total confirmed cases. Apart from this we have collected the data of the active cases too. The number of active cases is found to be 6,390,508. All of these cases were not the critical or serious cases of the COVID-19. Only 1% of active cases i.e. 64,666 numbers of cases were critical and remaining 99% of the total active cases i.e. 6,325,842 cases were in mild condition.

From the data survey of different sites of COVID-19, we used the data present on the site of worldmeters.info/coronavirus. The output of data survey showed the top 10 countries which had been infected the most by COVID-19 like USA, Brazil, India, Russia, South Africa, Mexico, Peru, Colombia, Chile and Spain with following numbered of confirmed cases as shown in table. A.

Also we had studied the growth of number of cases till date and found that on January 22, 2020, the total confirmed cases were only 580 which was increased to 1M by April 02, 2020 i.e. within 70 days and later cases reached from 1M to 10M by June 27, 2020 i.e. within 86 days and final data has now reached to the 20M cases by Aug 09, 2020 i.e. within 43 days worldwide. This data showed that the number of confirmed cases has increased which showed that the cases growth is more at present then it was in starting of pandemic.

Similarly we have made data study of the India separately and found that on Feb 15, 2020, there were 3 confirmed cases which got increased to 1M by July 16, 2020 i.e. within 151 days and cases reached to 2M by Aug 06, 2020 i.e. within 21 days. The data of the cases increment in India showed that there had been exponential growth of cases to reach from 1M to 2M cases. (14,15)

The data study for the SAARC nations related to the total confirmed cases and the case fatality were done from the Johns Hopkins Coronavirus information center site. Upon the study of the COVID-19 cases, we observed that data present on the site in India had the maximum number of confirmed cases which was the

78% the total cases of the SAARC region and Bhutan has the least number of confirmed cases i.e. 108 with zero death till date. Also we found that the case fatality was maximum for the Afghanistan i.e. 3.5% although the

number of confirmed cases is far more of India but case fatality of India was only 2.0%. The least case fatality was of Bhutan i.e. 0% as there had not been reported the death of confirmed cases patient till date. (16)

Table 1. Top 10 countries infected by COVID-19 with total number of confirmed cases (14)

Country	Confirmed case
USA	5,199,444
Brazil	3,035,582
India	2,214,137
Russia	887,536
South Africa	559,859
Mexico	480,278
Peru	478,024
Colombia	387,461
Chile	373,056
Spain	361,442

Table 2. SAARC region COVID-19 confirmed cases and case fatality data (16)

Country	Confirmed case	Death	Case Fatality
Afghanistan	37,054	1,312	3.50%
India	2,153,010	43,379	2.00%
Pakistan	283,487	6,068	2.10%
Bangladesh	255,113	3,365	1.30%
Nepal	22,592	73	0.30%
Sri Lanka	2,841	11	0.40%
Maldives	4,898	19	0.40%
Bhutan	108	0	0%

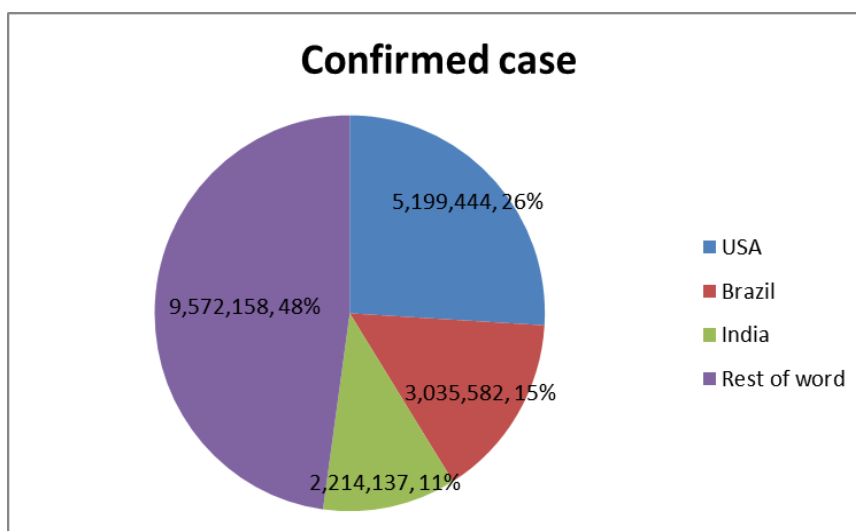


Figure 3. Comparison of top 3 infected countries with rest of world (14)

4. Herd Immunity for COVID-19 Pandemic

Once the child is born, they are always susceptible to various infections as they are continuously exposed to the various pathogens present in the environment whose main activity is to live and replicate in the host body. However there are number of pathogens which are essential of the health of the human begins present in the different parts of the body like in mouth, GI Tract, etc. (17)

To combat with these causative pathogens body had the well-known defense mechanism system present in the

body known as the Immune system. These immune system response against the pathogens and provided the protection against the infection. This ability of the body to response against the pathogen is dependent upon the individuals and is known as the immunity of the particular individuals. (17)

There are two types of immunity principally present in the human body. These are the a) Innate Immunity and b) Adaptive Immunity. Innate immunity system are the all aspects of the host’s immune defense mechanisms that are encoded in their mature functional forms by the germ-line genes of the host. Also the adoptive immune

system manifests exquisite specificity for the target antigens which are primarily based on the antigen-

specific receptors expressed on the surfaces of T- and B-lymphocytes.

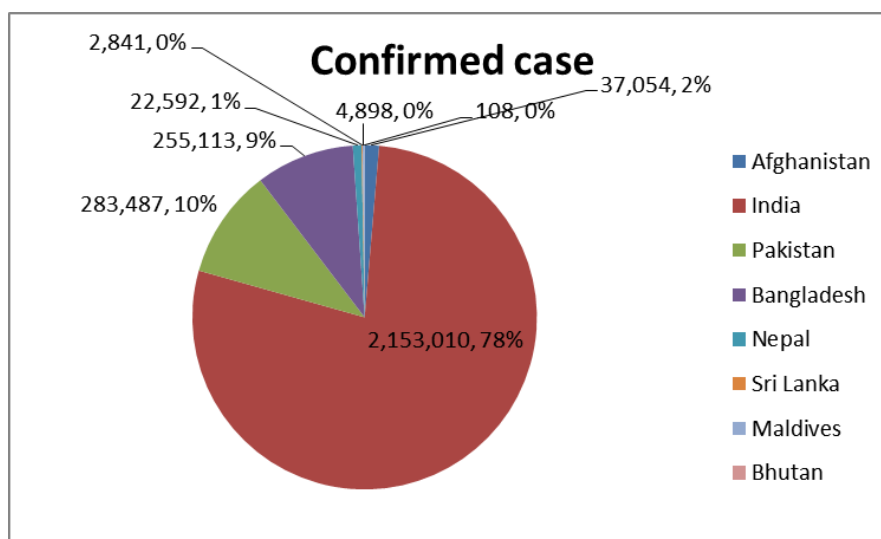


Figure 4. SAARC region Confirmed Cases of COVID-19 (16)

The innate and adoptive immunity system showed the defense mechanism action against the pathogens in combined or the dual action. Where the innate immunity acted as the first line of defense system of body in combat with pathogens. And also the adoptive immunity showed the response on later stage of the combat of pathogens. The combine response of the adoptive and innate immunity showed the fully effective immune response. (18)

In the cases of the global pandemic of infectious disease, herd immunity is the principal approached of the controlling the pandemic situation. As per the Association for Professional in Infection Control and Epidemiology, Inc. (APIC), the herd immunity had been defined as the community immunity which occurred when the high percentage of the community had been immune to a disease through the vaccination or prior illness which made the spread of that disease from person to person unlikely. (19) Dowdy et.al. (Johns Hopkins Bloomberg School of Public Health), had illustrate the herd immunity like this, if 80% of the population had been immune to a virus, four out of every people who encountered someone with the disease won't get sick and won't spread the disease any further. In that way, the spread of infectious disease had been kept under control. Depending how contagious an infection is, usually 70% to 90% of population needed immunity to achieved herd immunity. (20)

The herd immunity which is achieved by the prior illness had been known as the Natural Herd Immunity whereas the herd immunity achieved by the vaccination had been termed as the artificial herd immunity. Artificial herd immunity is achieved by mass vaccination programmed in the given population against the infectious disease which is known as the immunization against the particular infectious disease. As per the WHO, immunization is the process whereby a person is made immune or resistant to an infectious disease, typically by the administration of a vaccine. (21)

The novel COVID-19 had been the pandemic infectious disease presently affecting the worldwide. There is numerous novel vaccines candidate under the clinical and preclinical trial for evaluating their efficacy and the safety to human. Also there had been numerous drug used under the drug repurposing strategies used for treatment of the COVID-19. In the absence of drug for the treatment and vaccine for immunization, the concept of herd immunity by natural process i.e. prior illness. (6)

The natural herd immunity development process is the complicated and high risk process for the control of the COVID-19 infection. This had been risky because the complete sets of data related to COVID-19 had been collected like whether the COVID-19 virus makes the human immune to future infection or not. To achieve the halt of the COVID-19 pandemic, the larger number of the population had to have prior illness or should be infected with COVID-19 virus to reach the herd immunity threshold. As per Mayo Clinic organization to halt the COVID-19 pandemic in the USA, 70% of its population should be infected with COVID-19 virus to reach the herd immunity threshold. Then only the concept of herd immunity for the control of the COVID-19 pandemic will be applicable. There will be the major problem in sector of the health by the increased number of cases of the COVID-19 and death number also increased due to COVID-19. These death number would be more than the normal death number because number of population would lost their life due to lack of health facilities and proper treatment for illness. (22)

The study had been in carried out for SAARC region related to the reproduction number of COVID-19 virus (R_0). These reproduction numbers of COVID-19 virus had been used for the calculation of predicted herd immunity threshold for the effective herd immunity protection to the population. The reproduction number of virus in SAARC region was found to be $R_0=1.33$ maximum for Pakistan and $R_0=1.07$ minimum for the Bhutan. Also from the study $R_0=1.279$ for the India was

found. Based on these reproduction numbers of COVID-19 virus, the possible confirmed, deaths, recovered and active cases were predicted for the SAARC nations. The prediction were for three term i.e. a) Short Term Prediction (20 days)

b) Mid-Term Prediction (90 days which will be reached on August 31, 2020)

c) Long Term Prediction (180 days).

On comparison of the present data of the confirmed cases and mid-term prediction data (on August 9, 2020), only India had crossed the predicted value of the study. Rest of SAARC nations had not crossed the predicted values data of the study and comparison of the actual data and predicted data had tabled in table C. (23)

Second approach of achieving the herd immunity in population is via administration of the vaccine which immunizes the body against the COVID-19 virus. Herd immunity developed via vaccine administration are

much safer and effective than natural herd immunity development process. This had been the safer process because vaccination against the COVID-19 virus doesn't causes the illness to the administered population and it provide the protection against causative pathogens. The vaccine shows the most effective immune response if it carried its defense mechanism via dual action i.e. first by production of the antibody to fight against the pathogens and the second by memory recognition of causative pathogens after long time via T-cell activity of immune system.

From the herd immunity study conducted in Spain, provided nationwide and the regional estimates of COVID-19 dissemination in Spain showed remarkable differences between higher and lower prevalence areas where the observation had been found that one in three cases of infection was asymptomatic which remained untested. As the prevalence estimate had remained low and this had been clearly insufficient to provide herd immunity. (24)

Table 3. Comparison of Mid-term prediction data of confirmed cases with actual confirmed cases (16,23)

Country	Mid-term prediction confirmed cases (till Aug 31, 2020, Dey et.al.)	Actual confirmed cases (on Aug 09, 2020, Johns Hopkins)
Afghanistan	297,264	37,054
Bangladesh	451,840	255,113
Bhutan	372	108
India	1,717,831	2,153,010
Maldives	5,970	4,898
Nepal	185,528	22,592
Pakistan	332,528	283,487
Sir Lanka	8,832	2841

5. Future prospective of nanotechnology in COVID-19 treatment

As there have been no single drug or the vaccines till date for the treatment of the COVID-19 diseases. Thus there is urge for the development of the new novel vaccines within a short period time. The vaccine development has been the prime importance in pharmaceutical sector because the novel COVID-19 has been the global pandemic cases. More than 20M people had already been infected by this infections. To safeguard of the people's health, there is need of herd immunity development in population. This herd immunity helps to break the chain of human transmission by providing indirect protection to uninfected people. (25)

For the development of herd immunity in the mass population, we need the safe and effective vaccines against the virus. Here comes the role of nanotechnology, for the treatment of COVID-19. The novel vaccines development and manufacturing process involves the nanotechnology from starting of virus identification and isolation to mass manufacture of the vaccines. The novel vaccines developed based on nanotechnology consists of an antigen i.e. the viral particulate in a nano scale range. Also these antigen could may be delivered via the use of Nano carriers or Nano particulate vaccine adjuvants. (25)

Some of the examples of novel vaccines developed based on nanotechnology principal are viral-vector based vaccines, virus-like particles and virosomes, liposomes based vaccines, calcium phosphate nanoparticles, etc. As per WHO, 13 Aug, 2020 there has been the 29 candidates of vaccine in the different clinical evaluation stages. Also 138 candidate's vaccine in preclinical evaluation stages for COVID-19 treatment. Most of these vaccines are developed based on nanotechnology in short period of time. From the report of vaccines status available by 13 Aug, 2020, there have been 6 candidate vaccines which had reached to phase 3 of clinical trial. All these vaccines had been developed based on the nanotechnology as showed in table 4. Among these 6 candidate vaccine, 3 are based on inactivated viral particulate, 1 on m-RNA and 2 based on the LNP-mRNA. (26)

With the help of nanotechnology the structural study and isolation of the novel Coronavirus has been possible in short period of time. These data had provided the much more information in regards to COVID-19 virus. Because of which the isolation of viral particles from viruses and modification in the virus structured had been catalyzed. Also these information had helped in the selecting most effective target in virus particle which leads to better binding with the antibodies produced in the host.

Thus the nanotechnology would be a much more efficient and safest way to delivery and discovered the

new vaccines for the COVID-19 treatment that in future will help to develop the herd immunity in the people. (25)

Table 4. Top six vaccine candidate for COVID-19 treatment with type of nanotechnology used in development and their clinical trial phase (26)

COVID-19 vaccine developer/ manufacturer	Type of candidate vaccine	Final stage of clinical trial
University of Oxford/ AstraZeneca	ChAdOX1-s	Phase 3
Sinovac	Inactivated	Phase 3
Wuhan Institute of Biological Product/ Sinopharm	Inactivated	Phase 3
Beijing Institute of Biological Product/ Sinopharm	Inactivated	Phase 3
Moderna/ NIAID	LNP-encapsulated mRNA	Phase 3
BioNTech/ Fosun Pharma/ Pfizer	3 LNP-mRNAs	Phase 3

6. Conclusion

From the study of various articles we came to conclude that, the COVID-19 is the global pandemic which causes the respiratory syndrome. Thus to break the transmission of infectious causative virus from human to human, there is need of development of herd immunity in community. Herd immunity is achievable to community level by the mass vaccination programmed. As result of this there urgent need of novel, safest and effective vaccines for the control of this global pandemic disease. The nanotechnology helps the development of vaccines in short period than the conventional approach of vaccine development. Thus the nanotechnology prospective can be further study in development of vaccine and virus genome.

Acknowledgements

We thank our friends Milan Basel, Anupama Singh, Ayushi Agrawal, Tejaswini A, Loith C and Jalapa Pradhan for their support and help done to prepare this review article.

Financial Disclosure statement: The author received no specific funding for this work.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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