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Adaptive Immune Responses to SARS-CoV-2 and Prophylactic Vaccines for COVID-19

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ABSTRACT

The world experienced the outbreaks of SARS and MERS in the past and now experiencing the pandemic of SARS-CoV-2. Initially the infection was linked to seafood market in Wuhan for that studies were designed and investigation were done to know about the intermediate host of

SARS-CoV-2. However, to date, there is no evidences that defines the SARS-CoV-2 specific relationship or association with animals and birds. The number of confirmed cases and deaths are rapidly increasing day by day, but unfortunately, we have no prophylactic agent till date. It is noted that individuals have strong immune system can wins the race from SARS-CoV-2. The host immunity is divided into innate and adaptive immunity. The innate immunity relies on the activation of interferon 1 and its downstream cascade mechanism. While the adaptive immune responses are cell mediated and greatly relies on the activation of T cells. T helper cells type 1 plays a dominant role in host adaptive immunity to any viral antigen. Antigen presenting cells (APC) activates the cytokines which act as an inducers of T cells responses. However,titer of neutralizing antibodies is directly proportional to T cell Reponses, higher the titer higher will be the responses. Receptor binding domain in spike S1 protein could be considered good vaccine antigen, as it contains regions which induces the production of neutralizing antibodies to prevent attachment of SARS-CoV-2 to ACE2. However, nucleic acid- based vaccine, RNA and DNA vaccine are the advance vaccine platforms against emergency infections. R_0 value of SARS-CoV-2 is 2.2 to 2.6 greater than 1 which means continued transmission can occur. As we have no vaccine and other prophylactic agents. So to reduce transmission, the reduction of R_0value less than 1 is must, for which more than half of the infections must be prevented or controlled.

Keywords: Host-pathogen interaction; Adaptive immunity; Prophylactic vaccines; SARS-CoV-2; COVID-19; T cells

Introduction

The SARS-CoV-2 stands for severe acute respiratory syndrome coronavirus type 2. The SARS-CoV-2 is a single stranded RNA virus and belong to family coronaviridae [1]. Coronaviridae consists of more than 40 viruses but this virus appears new. The world now experiencing the pandemic of COVID-19 as it already experienced the outbreaks of SARS and MERS. These viruses found new at his outbreaks era and have a zoonotic origin. The COVID-19were first reported in Wuhan China and respiratory related illness were reported in infected patients [2]. Later on the genome were fully sequenced which revealed its similarity with SARS-CoV and

MERS-CoV and it became the member of Beta coronaviruses [3]. The transmission rate of SARS-CoV is high as compared to its mortality rate. The infection spread from region to region with in china and now spread throughout the world and became a pandemic [4]. As of May 8th 2020, there are 3.85 million confirmed cases and 270 thousand deaths reported worldwide due to COVID-19 infection. From the day 1st scientists and related researchers trying to get rid of this pandemic by development of vaccine but still the efforts are going and there is no vaccine. In this situation the strong host immunity is the only weapon to counter COVID-19. When the virus get entrance to host it binds with ACE 2 receptor of Alveolar type 2 cells, at this stage virus experiences the innate and adaptive host immunity [5]. The successful activation episodes of interferon type 1 and its downstream cascade "cytokine storm" slows down the viral replication and provide power of combat. Successful innate immunity activates plasma B cells to produce antibodies and memory cells for future recurrent infection of SARS-CoV-2. The adaptive immunity is greatly relies on T cell activation and the induction of CD8+ and CD4+ T cells [6]. Vaccine uses some attenuated viral antigens viral which work as an immune boosters. Thus the antibodies start to produce and host immune system become able to fight with virus. In case of SARS-CoV-2 the DNA, mRNA and other inactivated vaccine are under development [7]. And hope so will be available soon. The current review article focuses on immunological side of SARS-CoV-2 and prophylactic vaccines for it.

Interaction between Host and Pathogen:

Initially the infection were linked to seafood market in Wuhan [8]. Studies were designed investigation were done to know about the intermediate host of SARS-CoV-2. However, to date,there is no evidences that defines the SARS-CoV-2 specific relationship or association with animals and birds. In a recent research it is revealed that the genetic sequences of coronavirus in pangolins and humans matches up to 99 %, it speculates that pangolins could be likely the intermediate host for SARS-CoV-2 [9]. In addition a study on six family members infected with SARS-CoV-2 recently travelled to Wuhan had no direct contact with seafood market. Even one of them didn't travel to Wuhan and found positive for SARS-CoV-2. It is concluded that the virus spreads by human to human transmission via droplets, sneeze, cough, talk and close contact [10]. In another study 200 patients out of 277 diagnosed positive and have never been exposed to close contact with infected patients and Wuhan seafood market [11].

World health organization already issued a Public health emergency of international concern alarm in response to the rapid transmission of COVID-19. Although the mortality rate of SARS-CoV-2 is far lower than SARS-CoV-1 [12]12 and MERS-CoV [13] as shown in (**Figure 1)**.

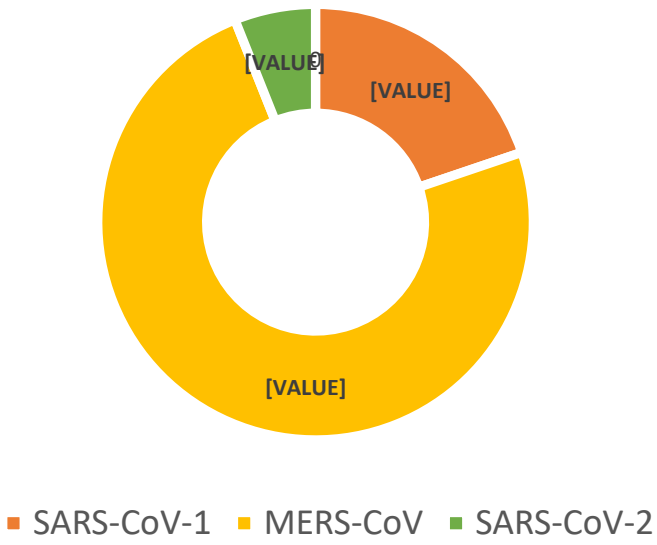

Figure 1: Mortality rate of SARS-CoV-1, SARS-CoV-2 and MERS coronavirus

A study in Germany revealed thatSpreading via asymptomatic route makes the SARS-CoV-2 virus more contagious in nature [14]. Average incubation period ranges from 2 to 11 days a mean of 6.4 days observed in 88 patients in Wuhan China [15]. The incubation periods of SARS-CoV-2 is similar to MERS and SARS. Incubation periods of 24 days much longer than 2 to 11 days were also reported [16].Experts in world health organization discusses the possible reasons of 24 days of incubation period of SARS-CoV-2 could be possible due to double expose or it just a outliner observation [17]. However tropism of SARS-CoV-2 is also possible. R_0 represents the average reproductive number of a virus, if R_0 value is greater than 1 continued transmission can occur and the R_0 value of SARS-CoV-2 is 2.2 to 2.6 [11,18].**Figure 2** shows R_0 values of some viruses. To reduce R_0 below 1 more than half of the infections must be prevented or controlled [19]. As compare to SARS-CoV-1 and MERS the R_0 of SARS-CoV-2 is much higher which implies that this virus is more contagious than other beta coronaviruses and preventive measures must be adapted to control it.

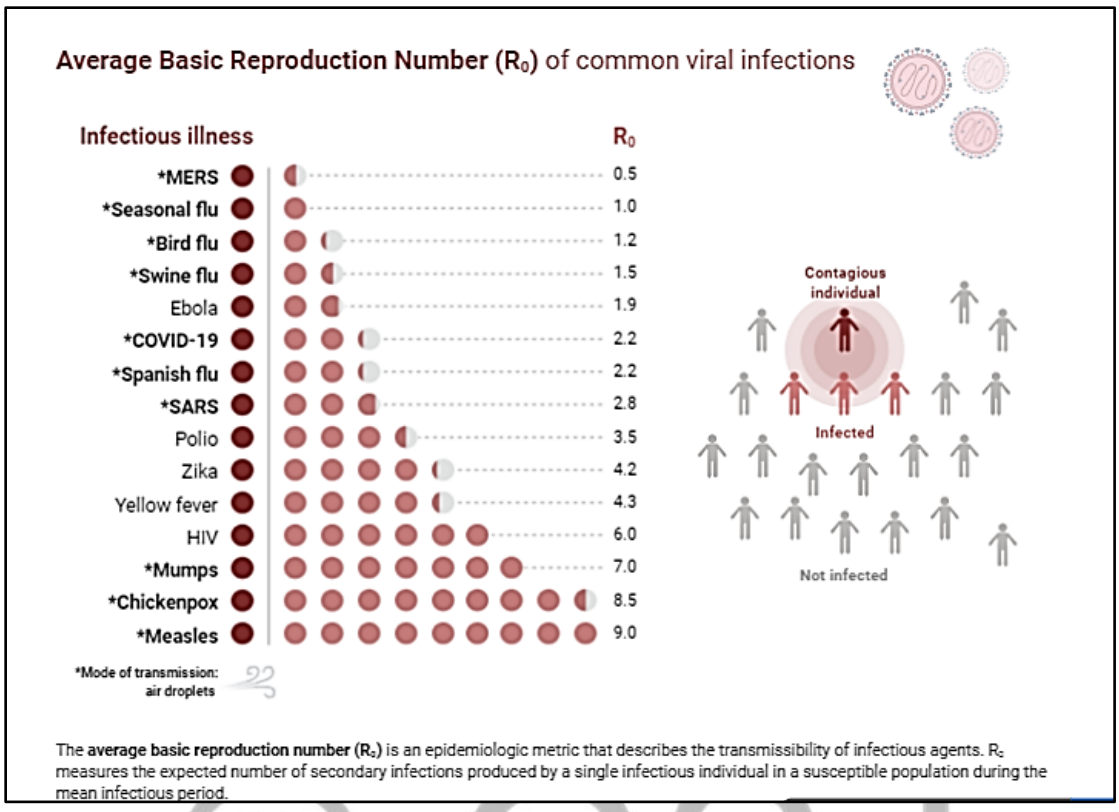

Figure 2: Average basic Reproduction number of common viruses. (Created in biorender.com)

The genome analysis revealed that spike S protein of SARS-CoV-2 have RBD region abbreviated receptor binding domain there for it attaches with ACE 2 and uses it as a cell receptor[20] as shown in (**Figure 3)**.In vitro experiments confirmed ACE 2 as a cellular receptor for SARS-CoV-2 [21]. Many wild animals expresses angiotensin converting enzyme 2 on their cell surfaces, it speculates and indicates the transmission between cross species rather than human to human transmission.

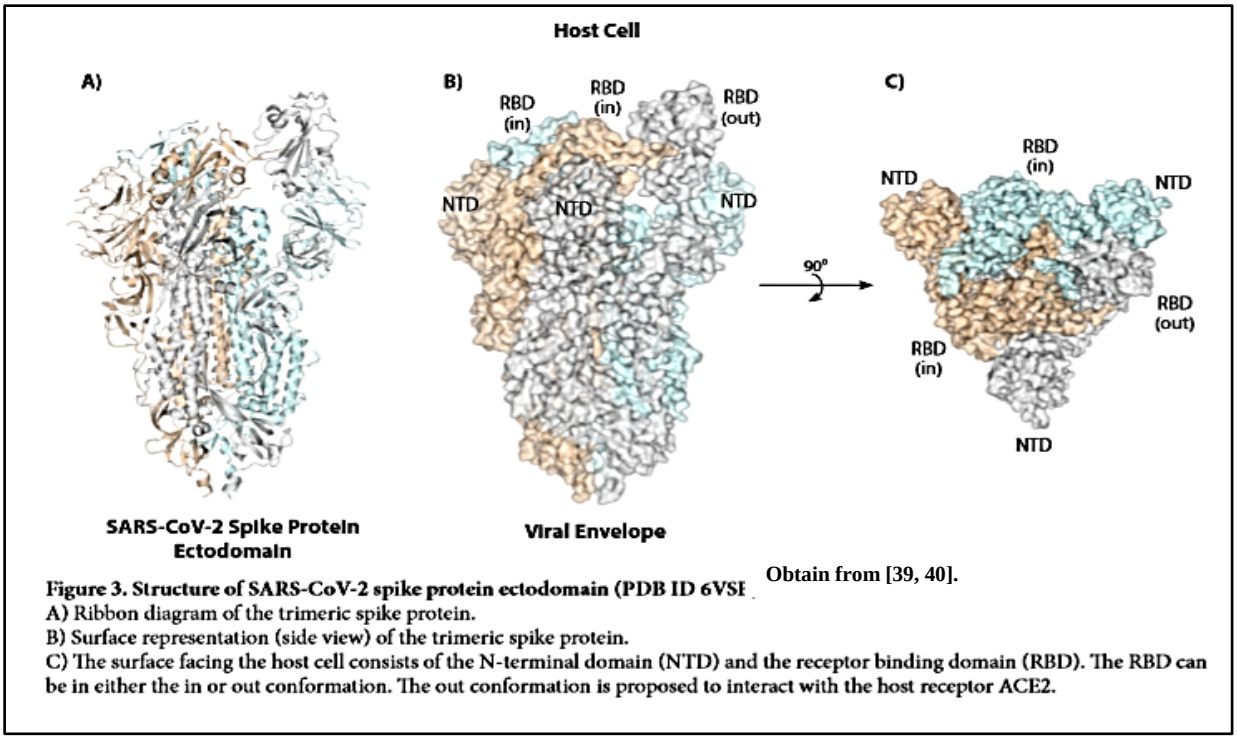

Figure 3. Structure of SARS-CoV-2 spike protein ectodomain (PDB ID 6VSB **Obtain from [39, 40].**
A) Ribbon diagram of the trimeric spike protein.
B) Surface representation (side view) of the trimeric spike protein.
C) The surface facing the host cell consists of the N-terminal domain (NTD) and the receptor binding domain (RBD). The RBD can be in either the in or out conformation. The out conformation is proposed to interact with the host receptor ACE2.

Figure 3. Structure of SARS-Co V-2 spike protein ectodomain (PDB ID 6VSB)

Adaptive Immune Responses:

The adaptive immunity also referred as acquired immunity. It is a subsystem of immune system consists specialized and systemic cells which processes to eliminate the pathogens from roots by preventing their growth. T helper cells type 1 plays a dominant role in host adaptive immunity to any viral antigen. Antigen presenting cells (APC) activates the cytokine which act as aninducers of T cells responses. The overall adaptive immune responses is based on T helper cells. The cytotoxic T cells directly kills the viral dominated cells. Antibody mediated immune system produce neutralizing antibodies against virus and limit the infection in later stage and prevents the reoccurring of infection in future. T and B cell surface proteins were largely plot for structural proteins of SARS-CoV M, N, E ad S [22].Sero conversion in SARS coronavirus were reported on day 4 of infection and after 14 days of infection.In some patient's immunoglobulin gamma (IgG) and other neutralizing antibodies are also reported after 2 year of infection (23).While in MERS the sero conversion were reported in 2nd or 3rd week of infection.In both cases delayed and weak immunity leads to severity of infection (22). In a recent study, one

patient infected with SARS-CoV-2 showed high specific immunoglobulin meu (IgM) at day nine of infection and after a time of two weeks switched to Immunoglobulin gamma (IgG) (24).

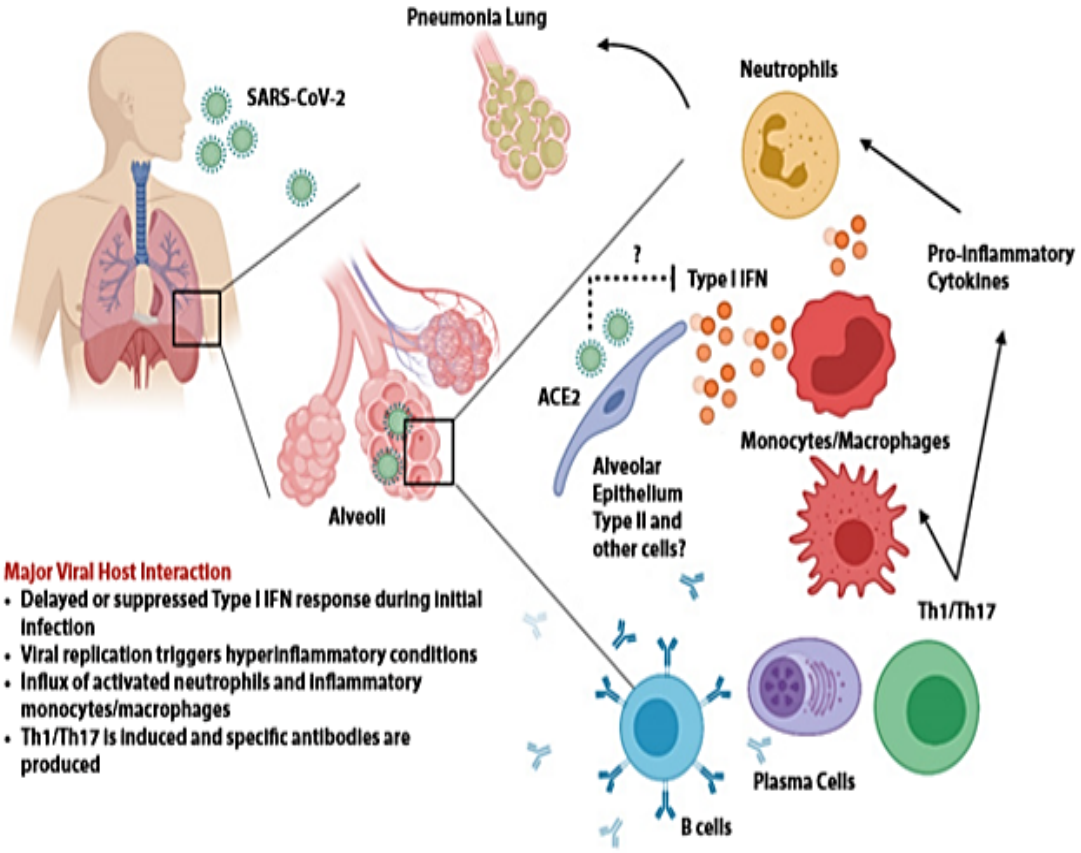

Figure 4 **Proposed host immune responses during SARS-CoV-2 infection. Obtain from [41].**

Aerosolized uptake of SARS-CoV-2 leads to infection of ACE2 expressing target cells such as alveolar type 2 cells or other unknown target cells. Virus may dampen anti-viral IFN responses resulting in uncontrolled viral replication. The influx of neutrophils and monocytes/macrophages results in hyperproduction of pro-inflammatory cytokines. The immunopathology of lung may be the result of the "cytokine storms". Specific Th1/Th17 may be activated and contributes to exacerbate inflammatory responses. B cells/plasma cells produce SARS-CoV-2 specific antibodies that may help neutralize viruses. The question marks indicated events that are still speculative or unknown. Figure is made with biorender (https://biorender.com/).

Five infected SARS-CoV-2 also showed some cross reactivity with SARS only.Moreover sera of some patients have neutralizing antibodies to COVID-19 suggesting the possible humoral immune responses (24). In case of SARS-CoV it was reported that in 128 samples the cytotoxic T cell responses were more frequent and high than T helper cells, CD8+ > CD4+. CD4+ T cells (IFNγ, TNFα, and IL-2) and CD8+ T cells (IFNγ, TNFα) were found in severe form of infection than mild. Th2 cytokines (IL-4, IL-5, and IL-10) were also detected in fatal group (25). Titer of neutralizing antibodies is directly proportional to T cell reponses, higher the titer higher will be

the responses. Approximately 70% of the T cell responses are against the structural proteins. The prompt rise of CD8+ T cells strongly correlates withsevere infection due to MERS (26). Neutrophils plays a crucial role in host immunity [27]. In light of the above information and evidences the Th1 type immune responses play a key role in controlling SARS and MERS and probably the SARS-CoV-2 as well.To prevent severe lung damage the CD8+ T cell responses must be controlled as severe strong responses are not good [28]. Most identified epitopes are concern with structural proteins of SARS and MERS in past. If these epitopes were mapped against SARS-CoV-2 and if successful it will lead to overlapping epitopes for three viruses. It will help in application of passive immunization. Convalescent sera from SARS and MERS recovered individuals will protect against SARS-CoV-2. It will also aid in designing of cross reactive vaccine.

Vaccines for SARS-CoV-2:

As of May 8, 2020 there are 99 vaccines in developmental stage and 40 are under human trails. Due to the rapid increase in confirmed cases and deaths the development of vaccine ignited and many researchers and scientist have started work on it as the outbreak arose. Antigen selection as a target and vaccine platform probably base on previous studies of SARS and MERS. Receptor binding domain in spike S1 protein could be considered good vaccine antigen, as it contains regions which induces the production of neutralizing antibodies to prevent attachment of SARS-CoV-2 to ACE2 (29-31). However, nucleic acid- based vaccine, RNA and DNA vaccineare the advance vaccine platforms against emergency infections.DNA vaccine was the first vaccine entered in clinical trials during outbreak of Zika virus, the clinical trial number was NCT02809443 [32]. mRNA vaccine is based on current advance technology and it has been considered an ideal candidate for boosting host immune system. This vaccine have improved stability and high protein translational efficacy [33, 34]. For the development of vaccine against SARS-CoV-2 basic and advance information are needed which includes investigation of valid and effective target antigens, route for administration, immune protection and immunization, animal models for trails, stability of vaccines, adjuvants, facilities for lab and large scale production, target product profile, pharmacokinetics and pharmacodynamics [35]. Collaboration between international organizations and transfer of technology between regions will also help in

development of an effective vaccine against SARS-CoV-2 [36, 37]. Clinical trials must be started in parallel with vaccine development. However the availability and safety of volunteers must be make sure [38].**Table 1** some shows some available treatments and under trial vaccines.

Drug	Classification	Mechanism of action against SARS-CoV-2	Vaccine	Phase
Lopinavir	HIV Protease Inhibitor	Suppress coronavirus replication by binding to enzyme M^{pro}	DNA	Phase II
Chloroquine	Antimalarial	ACE2 cellular receptor inhibition, inhibition of viral enzymes etc	Viral vector	Phase I
Hydroxy chloroquine	Antimalarial	inhibition of viral enzymes, virus assembly, fusion of the virus etc	Subunit	Preclinical stage
Azithromycin	Macrolide Antibacterial	Inhibition of mucus hypersecretion, decreased production of ROS, accelerating neutrophil apoptosis, and blocking the activation of nuclear TF.	Inactivated	Preclinical stage
Remdesivir	Nucleoside Analogue	Inhibitor of RNA-dependent RNA polymerases (RdRps)	Live-attenuated virus	Preclinical stage
Tocilizumab	Interleukin-6 (IL-6) Receptor-Inhibiting Monoclonal Antibody	Inhibits IL-6-mediated signaling by competitively binding to both soluble and membrane-bound IL-6 receptors.	Virus-like particles	Preclinical stage

Table 1: Some available options of treatment and under trial Prophylactic Vaccines

Conclusion

By observing similarities between SARS-CoV-2 and past outbreaks of coronaviruses, a large number of striking features and characteristics arise its own. COVID-19 causes serious to mild symptoms, it definitely somehow correlates with the immune responses. As young population have probably strong immunity therefore the mortality in adult age is low than old age population. The interaction of SARS-CoV-2 with host immunity may provide help in that how the disease get worsen and why some individuals have mild and some have serious symptoms. Moreover the study of immune responses correlates the long term immunity and help in designing of prophylactic and therapeutic vaccines for future.

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Conflict of Interest

Authors declare no conflict of interest.

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