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Short Communication

Are We Any Closer for a Safe Vaccine to be Launched-Experience of Phase 3 Trials of Certain Vaccines with Immune Responses in COVID-19 with a 3rs Wave in Most Countries Escalating SARS-CoV2-Patients

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Earlier having reviewed structure and treatment (Figure 1) options of COVID-19 secondary to SARS-COV2 [1-5], still the pandemic instead of getting controlled is on a rise and urgent need of a vaccine is required with the 3rd wave having attacked the world, here we discuss important points regards to getting insight of disease pathogenesis along with advantage of bridge therapies, like hyperimmune globulin along with convalescent human plasma besides developing vaccines, antivirals and monoclonal antibodies. Just 11 months back knowledge was not there. Here we sum up phase 3 trial of vaccines-status.

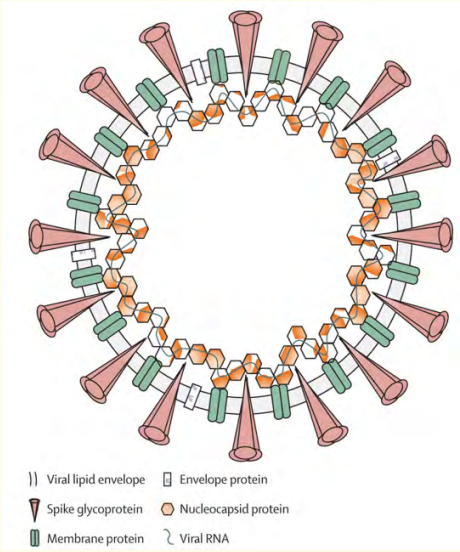

Figure 1: Courtesy ref no-6-The structure of the SARS-CoV-2 virion.

Once number of SARS-COV2 patients increase, identification, analysis as well as getting insight about immune response to SARS-COV2 infection becomes necessary (Figure 2). Very little information of post infection immunity to SARS-COV2 as well as biological, genetic factors=>broad spectrum of disease is queried. Results point to uncoordinated or partially neutralising antibodies, as well as responses from CD4+ as well as CD8+T cells might correlate with COVID severity, with age being a risk factor [5]. Knowledge of duration of immunity to SARS-COV2 infection, as well as targets of B cell as well as T cell responses, can aid in continued development of succeeding generation of new vaccines as well as Treatment.

Current knowledge-humoral and cellular immunity to SARS-COV2 in human-applications to vaccine.

Humoral immunity to SARS-COV2

Modulated by antibodies directed to viral surface glycoproteins, basically the spike glycoprotein as well as nucleocapsid protein (Figure 3). These antibodies neutralise viral infections of human cells as well as tissue expressing ACE2.

The 180kda spike glycoprotein possesses 2 subunits (like N-terminal S1 as well as C terminal S2) as well as is thought to be significant antigenic determinant that can stimulate a protective immune response [6] S1 subunit holds RBD, residues 331-524) that modulate viral binding to functional ACE2 receptors on susceptible cells as well as is the major target for SARS-COV2 neutralizing antibodies. Main part of neutralizing antibodies is antigen binding as well as crosstalk with cells bearing Fc-γ receptors for manipulation of

subsequent immune response. Lot of IgG responses against SARS-COV2 proteins (like nucleocapsid protein) S1, ORF9b, nsp5, as well as others; figure 3, have been found in convalescent serum samples from patients who have recovered from COVID 19 by utilization of SARS-COV2 proteome microarray technology [9].

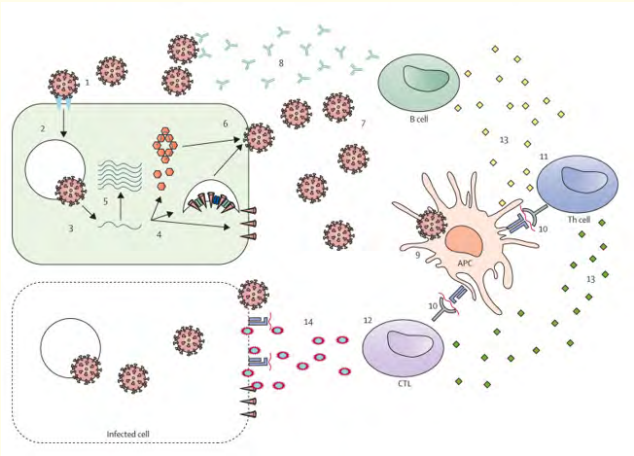

Figure 2: Courtesy ref no-6SARS-CoV-2 infection and the development of immunity.

The illustration depicts the major steps in the viral lifecycle and in the development of immune responses. (1) Attachment of the SARS-CoV-2 virion to the cell surface via interactions with the ACE2 cellular receptor. (2) Entry into the cell. Viral proteins can be recognised by pattern recognition receptors (eg, TLR3, TLR4, and TLR7), leading to the release of danger-associated molecular patterns, the inflammatory response, and the activation of innate anti-viral pathways. (3) Membrane fusion and release of RNA into the cell. (4) RNA translation to produce viral proteins. (5) RNA genome is copied and attached to the nucleocapsid protein. (6) Assembly of daughter SARS-CoV-2 virions. (7) Recognition of the spike glycoprotein and nucleocapsid protein (structural proteins) by the B-cell receptor. (8) B cell produces spike glycoprotein-binding antibodies and neutralising antibodies targeting the RBD region of the spike glycoprotein. (9) Viral uptake by APCs. (10) Presentation of antigens, including epitopes from structural and non-structural proteins, to T cells. (11) Activation of Th cells. (12) Activation of CTLs. (13) Th cells produce cytokines (mainly IFNγ, IL-2, and TNFα). (14) CTL recognition and killing of infected cells. ACE2=angiotensin-converting enzyme 2. APC=antigen-presenting cell. CTL=cytotoxic T lymphocyte. RBD=receptor-binding domain. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. Th= T-helper. TLR=toll-like receptor. TNF=tumour necrosis factor.

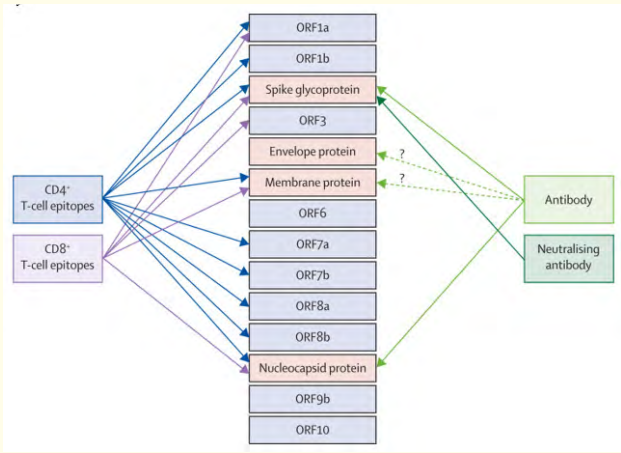

Figure 3: Courtesy ref no-6SARS-CoV-2 proteins targeted by adaptive immune responses.

The four structural proteins are shown in the red boxes. Non-structural proteins and accessory factors are shown in the blue boxes. Arrows link antibodies to the viral proteins they target and identify viral proteins shown to contain epitopes targeted by CD4+ T cells or CD8+ T cells. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Functional neutralizing antibodies particular to SARS-COV2 which get formed after infections, vaccination or both (anti spike glycoprotein as well as anti receptor binding domain (RBD)) are believed to be significant for viral neutralisation. Due to this, antibodies titres might be good biomarkers for the protective efficiency of antibodies as well as successful humoral immune responses following SARS-COV2 exposure. Actually, a robust association (r range 0.87 - 0.94) among neutralizing antibodies responses against spike glycoprotein as well as nucleocapsid protein and RBD proteins picked by plaque neutralization test as well as detected by ELISA has been documented in patients with PCR confirmed COVID 19. IgG, IgM, as well as IgA responses to SARS-COV2 cysteine like proteases have further been documented in COVID 19 patients as well as these responses associated with antibody titres to nucleocapsid protein. High quality studies evaluating the duration of protection of functional neutralizing antibodies as well as potential for re infections are required in large cohorts of patients with COVID for insight as well as property of SARS-COV2 specific immunity.

Maximum patients with COVID 19 or who are convalescent possess virus- specific IgG, IgM, as well as IgA responses in the days

following infections, pointing that antibodies modulate protective immunity towards SARS-COV2. Total kinetics of this antibody response against SARS-COV2 are akin to those found for SARS-COV1, that have the property of severe seroconversion (of IgG, IgM) 7 - 14 days after the onset of symptoms as well as antibodies amounts persisting for weeks-months following infection as well as viral clearance. In a longitudinal study-finding the kinetics of spike glycoprotein-particular antibodies in COVID 19 patients, observed that IgA antibodies got formed early (in the 1st week) as well as peaked in amounts at 20 - 22 days, while IgM, antibodies attained high titres at 10 - 12 days which ultimately reduced 18 days following onset of symptoms [11]. In a seroprevalence study evaluating IgG responses to spike glycoprotein in 40 patients with COVID 19 following symptoms onset documented that escalation of IgG titres occurred during 1st 3 weeks as well as started to decrease by 8 weeks [15]. In patients having mild symptoms of COVID 19, a rapid fall of RBD -specific IgG titres occurred during 2 - 4 months has been seen in multiple studies, pointing that humoral immunity induced via SARS-COV2 might not last long enough following mild disease [16]. Similarly, for antibodies responses towards SARS-COV2 nucleocapsid protein.

Cellular immunity to SARS-COV2

Earlier response to SARS-COV2 have mostly been case reports with smaller amount of patients, that have pointed that the proportion of CD38+, HLA-DR+ T cells (both CD4+ as well as CD8+T cells) escalate during the initial 7 - 10 days of COVID 19 symptoms as well as start to return to baseline around day 20. SARS-COV2 specific T cells express perforin 1 as well as granzymes upon in vitro restimulation with viral antigens. In certain reports, but not rest, the escalation in the percentage of SARS-COV2 specific T cells appeared to associate with the disease severity (as well as this observation represented a Significant query with no answer that would influence vaccine formation. Serious illness has also been associated with the decrease in peripheral CD4+ as well as CD8+T cells counts as compared to nonserious illness, pointing an association among disease severity as well as the size of the Cellular immune response, but larger studies are essential for supporting an association.

T cells responses to peptides obtained from SARS-COV2 spike glycoprotein was analyzed by Braun., *et al*. [6], utilizing the expression of activation markers (4-1BB ligand receptor as well as CD40-L) for finding epitope-particular CD4+ T cells. HLA-DR+ as well as CD38+ activated T cells particular to the spike glycoprotein were observed in 15 (83%) of 18 patients with COVID 19. Significantly, Braun., *et al*. [6], isolated T cells reactive to spike glycoprotein 24 (35%) of 68 healthy participants who did not test positive for COVID 19. The part of these pre-existing SARS-COV2 reactive cells in not known but, Braun., *et al*. [6], posited that the presence as well as absence of these cells might result in the different clinical presentations of COVID 19.

HLA prediction algorithms as well as peptides mega pools were utilized by Griffoni., *et al*. [6], for isolating SARS-COV2-particular T cells in 10 patients with COVID 19 as well as 11 healthy unexposed control participants. Virus- particular CD4+ T cells responses were observed in 7 (70%) patients with COVID 19 as well as Virus- particular CD4+ T cells responses were observed in all 10 patients with COVID 19, that further pointed that most persons can form T cells responses to SARS-COV2. Recognizing SARS-COV2 antigens via preexistent as well as cross reactive T cells formed at the time of earlier infection. With human coronaviruses may further aid in usual presence of T cells reactive to SARS-COV2 in patients with COVID 19. CD4+ T cells The responses mainly comprised of T-helper 1 (Th1) cells having the properties of high amounts of interferon gamma (IFNγ) liberation as well as of preference for structural spike glycoprotein, the membrane protein, as well as the nucleocapsid protein (in this order, though non-structural protein (nsp3, nsp4 as well as ORF8) also got targeted. CD8+T cells responses particular to SARS-COV2 generation of IFNγ as well as TNF-α are also indicative of a responses skewed towards Th1 cells. This immunodominance pattern was separate from Th1 cells responses, but this pattern further demonstrated propensity for structural protein as compared to non-structural protein (preference order; spike glycoprotein, the membrane protein, nsp 6 as well as the nucleocapsid protein, ORF8, as well as ORF3; figure 3). Unexposed donors also possessed CD4+ T cells (6 (60% of 10) as well as CD8+T cells 4 (36%) of [11] reactive to SARS-COV2 peptides, pointing that T cells cross reactivity might be common. In 42 patients, having recovered from COVID 19 as well as 19 uncontrolled controls, utilizing an overlapping peptides pool strategy covering each viral protein, other than ORF1 had T cells responses analyzed by Peng., *et al*. They further observed that both CD4+ T cells as well as CD8+T cells responses got skewed towards Th1 cells with the generation of IFNγ, IL-2 as well as TNF-α as well as observed that spike glycoprotein was immunodominant. In both studies, strength as well as breadth of the immune response was enhanced in patients with severe dis-

ease as compared to patients with milder disease, with marked inter-person-differences in the response, but, a few peptides got targeting commonly as compared to others. Deeper experiments on T cells responses in 203 patients with COVID 19 observed that viral particular T cells showed an activated, cytotoxic phenotype at the time of infection, while viral particular T cells analyzed during convalescent phase possessed a memory phenotype as well as were poly functional, with both CD4+ T cells as well as CD8+T cells expressing IFNγ,IL-2 as well as TNF-α [17]. Significantly, T cells responses were observed in persons recovering from mild COVID 19 in whose case enough antibodies responses to SARS-COV2 were not seen.

In the 1st documentation on SARS-COV2 vaccine (an adenoviral serotype-5 vectored vaccine expressing the spike glycoprotein),in humans T cells responses in the 108 vaccine recipients got measured by an IFNγ enzyme -linked immunospot as well as intracellular cytokines staining following stimulation with overlapping spike glycoprotein peptides. T cells responses from CD4+ T cells as well as CD8+T cells were observed 14 as well as 28days following vaccination. The T cells that responded further, generated IL-2, TNF-α or both. CD4+ T cells had >possibility of being polyfunctional as compared to CD8+T cells. Pre vaccination T cells responses towards SARS-COV2 spike glycoprotein were minimum to negligible in all patients, pointing that this population did not have cross reactive T cells immunity. The degree of cross reactivity among T cells responses towards SARS-COV1 as well as SARS-COV2 has to be observed.

T follicular helper cells (Th) cells responses are key for the generation of massive humoral immunity via the generation of germinal centres as well as providing co- stimulation (like CD40-CD40-L crosstalk) as well as cytokines (like IL21) to B cells. In a post-mortem study of persons who died of COVID 19 observed lack of germinal centres as well as no BCL6+Tfh cells, pointing to an insufficient activation of the Tfh response, being a probable mode for the pitfalls in durable antibodies responses to SARS-COV2.Nevertheless, a single cell RNA sequencing study of the CD4+ T cells responses to SARS-COV2 observed an enhancement of degree of Tfh cells in patient with severe disease as compared to patient with mild disease. Meckiff., *et al*. [6], documented that cell clusters enriched in SARS-COV2 –particular CD4+ T cells expressed canonical Tfh genes (like CXCL13, IL-21, as well as BTLA), pointing that SARS-COV2 - infection.

Does result in, escalated generation of Tfh cells. Risk factors for severe COVID 19 are also correlated with > amounts of T helper (Th17) cells, as well as proof exists that collection of Th17) cells can result in the enhanced inflammation observed in COVID 19.

Lot of early reports have observed a statistically significant decrease in T cells counts in COVID 19 patients with extra studies documenting functional exhaustion of the rest of the T cells persisting. Nevertheless, the above mentioned studies, which evaluated the cellular immune response particular to SARS-COV2-did not document similar observations, although CD4+ T cells responses are definitely have robust as compared to CD8+T cells responses. Probably variation in study timing (like variation in study timing (like during acute illness vis a vis convalescent phase), differing definitions of mild as well as severe disease, as well as other factors adding to the conflicting outcomes.

Laing., *et al*. [6], tried to isolate an immune signature in - COVID 19 patients which could get utilized to aid in clinical management. Additionally, besides generation of humoral as well as Cellular immune responses particular to SARS-COV2, Laing., *et al*. [6], found multiple extra properties which could separate the COVID 19 patients from the patients who had recovered from COVID 19 as well as nonexposed patients controls that included the upregulation of IL-6, IL-8, IL-10, as well as C-X-C motif chemokine 10; rapidly cycling T cells that expressed exhaustion markers (PD-1 as well as HAVcr-2) depletion of both αβ T cells as well as γδ T cells, reduction in natural effector as well as CD5+ B cells, enhanced neutrophil amounts, as well as shift in frequency of CD11+ as well as CD11- myeloid dendritic cells. More evaluation of these changes might give enhanced understanding of disease presentation. Targeted Treatment for reversing or reducing these alterations (like suppression of inflammatory cytokine generation) could also help in clinical Treatment.

In total, the present results documented that CD4+ T cells as well as CD8+T cells responses take place in major patients with SARS-COV2 within 1 - 2 weeks of symptoms onset as well as generated Th1 cytokine mainly. The periodicity of CD4+ T cells targeting to the spike glycoprotein associated with the neutralizing antibodies titres, pointing that the T cells responses might also differ amongst certain persons possessing various disease severities. 2 small studies have further pointed that certain persons exposed to SARS-COV2 form particular T cells memory responses once their is lack of humoral immune response s pointing that cellular immunity

might be stimulated in lack of humoral immune response. The aid of cellular immunity to protection against COVID 19 is not clear at present, Nevertheless, a balanced immune response made up of high titres of neutralizing antibodies and Th1 –biased T cells would probably be best. The part of CD8+T cells responses are stronger in pts possessing milder disease patient as compared to, patients possessing severe disease [6]. More research into the cellular immune response to SARS-COV2 as well as COVID 19 vaccines would be essential for testing this posit. Certain but not all, of the phase 1/2 trials of COVID 19 vaccines evaluated cellular immunity, thus this posit cant be fully answered.

SARS-COV2 vaccines

Vaccines against SARS-COV2 which evoke protective immune response are key to the avoidance as well as amelioration of the morbidity as well as mortality secondary to SARS-COV2 infection. Present insight points that a balanced humoral and Th1 –biased cellular immune response might be significant for avoidance of COVID 19 and prevention of vaccines escalated disease. Different candidate vaccines are being formed and evaluated, that include nucleic acid vaccines, inactivated virus vaccines, live attenuated vaccines, protein or peptide subunit vaccines and viral vectored vaccines. Every approach has its advantages and disadvantages-already reviewed in [6].

Front runner candidates are all given by in route, hence focus is on analysis of immune response in the blood instead of those in the mucosal surfaces. The part of mucosal immunity does not have to be ruled out and lot of intranasal vaccines formulations are being evaluated.

By Aug 2020, lot of multiphase phase3 clinical vaccines trials, each one including tens of thousands participants, had been initiated in different geographical parts (like USA, UK, UAE, Morocco Argentina, perum. Brazil, Indonesia, Russia, China, South Africa). Interim results from these trials are anticipated to be available by end of 2020 and will give 1st indication as well as efficiency as well as safety of COVID19 vaccines. Significantly certain phase3 phase 3 trials are designed as well as statistically powered around the pr endpoint of avoiding severe COVID 19. This design could cause problems in the sense of enough no of participants. In USA, FDA has given guidance pointing that a COVID19 vaccines would need to protect a min of 50% of vaccinated people for defining efficacy. Additionally, defining safety would be limited in statistical power in max trials, especially for uncommon side effects. Significantly few trials include people < 18yrs as well as likely to enrol sufficiently large amt of people > 55yrs (especially those in congregate living conditions) and all present trials exclude women who are pregnant. Lot of mutations of SARS-COV2 have been found, thus vaccines generation could get obstructed if the virus later evades immunity to the spike glycoprotein utilized to manufacture vaccine.

Review of current candidates in phase 3 trials.

Astra zeneca

Oxford University (Oxford, UK) and Astra Zeneca have generated a chimpanzee adenovirus -vectored investigational vaccines (Ch Ad Ox1/AZD122) encoding the spike glycoprotein of SARS-COV2. This vaccines demonstrated both immunogenicity as well as protective efficiency in nonhuman primates giving a prime boost vaccination schedule (2.5 x 1010 viral particles in every dose, with the 2nd dose given 28d following 1st) [9]. A phase ½ trial with 543 persons getting the AZD122 vaccine tested a prime (5 x 1010 viral particles) as well as a prime- boost (2.5 x 1010 viral particles) schedule. The study demonstrated the humoral responses, having the properties of anti-spike glycoprotein IgG and neutralizing antibodies, IFNγ T cells responses in maximum recipients following the 1st dose of vaccine as well as extra escalation of humoral immune responses in in vaccine recipients were akin to those seen in convalescent plasma from patients having recovered from COVID 19. Side effects were pain as well as tenderness at injection site, chills, fatigue, fever, headache, malaise, muscle aches and nausea were usually mild and mostly took place within 4 - 5 days of vaccination. An amendment of trial protocol for inclusion of paracetamol, that decreased local; and systemic vaccine reactions. The phase ½ trial was briefly with held following a participant developing neurological symptoms, that were later correlate with multiple sclerosis. A large phase 3 trial of the AZD122 vaccine that included 30, 000 adults (20, 000 vaccine recipients with 10,000 controls) started in august 2020, in a lot of worldwide areas. The phase 3 trial was temporarily again paused secondary to a vaccine recipients developing transverse myelitis. Despite UK trial restarted shortly after this halt, as of 5th october 2020, the US trial has not yet resumed. This vaccine needs registration, that can create problems for utilization in low income countries.

Moderna

Moderna and NIH jointly formed a mRNA-dependent vaccine (mRNA-1273) made of a sequence-optimised mRNA that encodes

the spike glycoprotein encapsulated in lipid nanoparticles [11]. Studies conducted in nonhuman primates have demonstrated the both immunogenicity as well as protective efficiency of the vaccine following 2 doses (10 µg or 100 µg) administered 4wks apart. In a phase1, dose- enhancement trial, this particular vaccine, stimulated both spike glycoprotein binding as well as virus neutralizing antibodies responses in recipients between 18 - 55 yrs age [12]. These humoral immune responses were akin to those seen in convalescent plasma from patients who had recovered from COVID19. Vaccine recipients further formed cellular immune response, basically biased towards CD4+ T cells. CD8+T cells were marginal, other than those in recipients of2 vaccination with the higher dose (100µg). No significantly safety concerns were observed with this vaccine, with mild local as well as systemic vaccine reactions, that were pain at injection site, chills, fatigue, malaise, and fever, occurring within few days of vaccination. A ph3 trial of mRNA-1273 was initiated in August 2020, in USA. This trial will include 18yrs and older, with (20,000 vaccine recipients with 10,000 controls. One probable issue for vaccine use is that a storage temp of -20^{0}C is needed.

Pfifer and Biontech

A series of mRNA based COVID19 vaccines formed. Early phase ½ trial [12] that tested 2 vaccines (BNT162b1, BNT162b2) in 45 participants point that BNT162b1, a lipid nanoparticle formulated, nucleoside-modified mRNA vaccine, stimulated RBD-binding IgG and neutralizing antibodies, with mainly mild adverse actions (pain at injection site, chills, fatigue, malaise, joint pain. Participants were 18 - 55 yrs-randomly assigned to get 2i/m doses separated by 21 days (either 10 µg, r30 µg or 100 µg) of BNT162b1 (given as 0. 5ml doses, stored at -800C). A 2nd dose of 100 µg of vaccine was not given due to enhanced reactogenicity. At day 21 following 1st dose geometric mean titres of convalescent panel RBD - particular IgG were measurable ranging, 534 u/ml-1778 u/ml were neutralizing antibodies. By 2 weeks after a 2nd dose geometric mean titres of neutralizing antibodies were 1.9 times > than the 10 µg vaccine dose and 4.6 times following 30 µg vaccine dose than the geometric mean titres of neutralizing antibodies of convalescent panel pointing the presence of Antibodies affinity affirmation [12]. Safety, cellular and humoral immune response, 2 weeks following 2nd dose of vaccine were evaluated here. Both BNT162b1, and BNT162b2 evoked same dose-based SARS-COV2 geometric mean titres of neutralizing antibodies in both younger (18-55yrs) and older (65-85yrs) especially, but BNT162b2 vaccinated persons had > CD4+ T cells. CD8+T cells responses against a spike glycoprotein and RBD as compared to BNT162b1, vaccinated participants. Since BNT162b2 vaccinated generated a breadth of T cells responses and had a favourable safety it was the candidate vaccine selected for testing in phase 3 trials. Storage at -80^{0}C, a fact which might cause problems. In about 44000 persons A phase 3 trial (18 - 55yrs) is occurring in USA.

Johnson and Johnson [13]

GAMALEYA [14]

Can Sino Biologics [15]

Sinopham [16] are others getting evaluated.

Multiple vaccine types need to be tested in separate populations (immunoimmature infants, children, pregnant women, immunocomprised and immunosenescent persons age ≥ 65yrs. Besides adaptive, there some data point trained innate immunity might have a part in COVID19 protection. Multiple clinical trials (like NCT 04327206, NCT 04328441, NCT 04414267 and NCT 04417335) are testing if unrelated vaccines like measles, mumps and rubella, BCG vaccine can evoke trained innate immunity and give protection from COVID19. Significantly genetic drivers of infection and vaccine induced cellular and humoral immune response at epitope level, characterising B cell response and T B cell response elicited by injection or vaccination. Safe licensing for immunoimmature infants, children, pregnant, women, immunocomprised and immunosenescent persons and nursing home residents needed. Till 5th oct 2020 no such studies done though UK is considering [6-8].

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