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LITERATURE REVIEW

Pros and Cons for COVID-19 Vaccination and Boost of Young Adults in Light of Recent Literature

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ABSTRACT

Many lives were saved in high-risk populations through the rapid development of COVID-19 vaccines. However, further mutation of new viral variants has reduced vaccine efficacy. Here we provide a review of the literature on pros and cons of vaccination and boost vs. naturally acquired immunity in young healthy adults. Our research indicates (1) being vaccinated, even after booster shots, demonstrates limits to protection from infection and spreading of the COVID-19 variants. (2) Young healthy adults predominantly develop mild or no symptoms after infection with SARS-CoV-2 variants, particularly Omicron, as such vaccination is not necessarily needed to protect young healthy adults. (3) Sequential vaccination with booster injections has been associated with reports of autoimmune complications. Complications not as commonly seen after natural infection. (4) Numerous assessments have revealed immunity imprinted through natural infection and durable protection against COVID-19 variants thereby supporting choice to natural infection in some. We conclude that for the young healthy adults, some of the risks and disadvantages afforded by vaccination prevail over the medical benefits. Moreover, Omicron as was observed, caused mild upper respiratory tract infection, and appeared to act in young healthy adults as an ideal "natural vaccine" to induce herd immunity, which in effect will diminish new variant development and may reduce duration of future pandemics in combination with vaccination of elderly and immune compromised.

INTRODUCTION

When COVID-19 first emerged, scientists, clinicians and politicians required rapid response. Much of initial management was empiric with limited validated consensus given the extensive novelty of the virus, our medical and scientific lack of prior experience and rapid worldwide pandemic advancement. Then based on the sudden spread to the unprepared elderly population, our first assumption was we were dealing with a deadly virus to all but that it could be halted via combined scientific, clinical and political effort. Today, Delta and Omicron variants are prevalent with Omicron rapidly advancing. However, open strategic discussion of management options are limited. We, thus, reviewed the published literature to address key questions in order to establish a strategic approach to booster vaccination or other management options for young healthy adults. Specifically, literature support was searched to address four questions. 1) Is there improvement in benefit to risk with mandated booster vaccination? 2) Can adequate herd immunity be provided solely by mass boost vaccination to spike protein? 3) Does natural immunity of previously exposed subjects add to support of herd immunity against COVID-19? 4) Are development of therapeutic measures as opposed to prolongation of continued sequential booster vaccination injection to original SARS-CoV-2 molecular spike protein sequence a more justified approach?

Study Justification of Supplemental Booster Vaccination

To start our review, we assessed data involving BNT162b2 justification for vaccination boost submitted as a supplemental to the approved Biologics License Application (BLA) of BNT162b2 on 08/25/2021. In this assessment, boost vaccination was extended following the primary two course vaccination approach. The study population included 300 patients (18-55 years old) who participated in the original Phase 3 labeling study and 11 (18-55 years old) plus 12 (65-85 years old) patients involved in Phase 1 testing of BNT162b2. These patients received a boost 6-9 months after completing their primary two dose regimen. Safety and immunogenicity data of the boost period was presented and compared to the prior two course vaccination response [1]. Short term safety of the post boost period compared to post two course vaccination did not appear different. Immunogenicity involving a subset of 210 of the 323 patients was more closely evaluated. Results showed elevated neutralizing antibody at 1 month post boost 3-4 times higher than 1 month post second of two vaccination regimens. Evidence of booster induced antibody increase of similar degree was later shown for JNJ-78436735 at a second BLA submission to FDA approved on 10/20/2021 [2]. Booster injection with either vaccine, however, did not demonstrate statistically significant clinical benefit [1, 2]. The focus for approval with both vaccines was improved immunogenicity involving short term neutralizing antibody titer rise to wildtype SARS-CoV-2 spike protein [1].

Severe symptomatic COVID-19 infection overall is demonstrated far less frequently in young healthy adults than in elderly, pre morbid or immune compromised patients [3]. Mortality globally of patients <40 years old to SARS-CoV-2 infection is between 0.01-0.25% [3, 4]. Mortality comparison from the labeling study between BNT162b2 vs. placebo involving "44,000" participants was recently updated at the FDA Advisory Committee meeting 09/17/2021 [1]. In the report to FDA, 21 BNT162b2 vaccinated patients died compared to 17 placebo patients over the same time period showing no difference in mortality. COVID Vaccine Adverse Events Reports (VAERS) from the CDC have been collected from first COVID-19 vaccine administration 12/11/2020 to 11/19/2021. Contained within these AE reports were 19,249 deaths and 97,561 hospitalizations related to vaccination toxic effect reported by medical caretakers [5]. The majority of deaths related to COVID-19 vaccination occurred within 2 weeks of most recent vaccination. The VAERS system however has many limits and does not validate cause and effect. However, CDC tracking of cause of death is also difficult given variation in definition of COVID-19 infection ranging from presumptive diagnosis of COVID-19 based on likely symptoms (prior to diagnostic testing, i.e., RT-PCR) [6] to RT-PCR diagnosis but with amplification cycles ranging up to 45 where false positive diagnosis is high [6]. Moreover, patients with multiple mortality involved comorbidities and just the presence of COVID-19 often were labeled "only" COVID-19 death [6].

Long term "controlled" follow up of the original BioNTec/Pfizer 2 dose label vaccine trial is also limited as only 7% of BioNTec/Pfizer participants reached 6 months follow up before the blind opened. Crossover from control group to off control with administration of BioNTec/Pfizer treatment

was provided for all of the control patients and 93% of them crossed over early to receive BioNTech/Pfizer vaccine. Long term follow up beyond 6 months and comparison to natural immunity against SARS-CoV-2 and early resistant viral variant evolution thus became ineffective [7, 8]. The lack of controlled long term follow up due to loss of crossover control patients compromised quality assessment of BioNTEC/Pfizer long term toxic evaluation. Including effect on an infrequent occurrence called "long COVID syndrome" [9], which involves prolonged fatigue, difficulty breathing, cough, join pain, concentration difficulties and other mild to moderate "feeling back to self" symptoms. Long COVID syndrome has limited treatment but may benefit from primary vaccination although it has not been studied post booster.

Cardiac Toxicity

Included in the VAERS reports of vaccination toxicity (12/11/2020 to 11/19/2021) are 23,974 cardiac events (9,546 heart attacks, 14,428 myocarditis/pericarditis events) [5]. The majority of myocarditis/pericarditis events registered in VAERS occurred in young healthy adults. A subsequent analysis by Oster et al [10], incorporating Medical Dictionary for Regulatory Activities definition of myocarditis, medical records review when available and further filtering via CDC screening and public health screening to verify separate CDC definition of confirmed myocarditis, still found 1,626 cases of myocarditis occurring within 7 days of COVID-19 vaccination between 12/2020 and 08/2021. Actual cardiac damage evidence by elevated troponin levels was demonstrated in 98% of cases. Median age of affected individuals was 21 years old and involved 82% males. Of particular concern was the observation that the percent occurrence from first to second vaccination was increased by more than double. Long term follow up at 3 or greater months after vaccination was not possible due to insufficient data. Independent of VAERS, Diaz et al [11] did a historical review of emergency visits and screened for myocarditis and pericarditis of patients not vaccinated during 01/2019 – 01/2021 (pre-vaccine) and compared to patients who were vaccinated (from 02/2021 – 05/2021, vaccine period) in the Providence Health Care System. Monthly number of cases of myocarditis (pre-vaccine period) was 16.9 (95% CI 15.3-18.6) per month and monthly number of cases post vaccine increased to 27.3 (95% CI 22.4-32.9) cases per month ($p<0.001$). Similarly, pericarditis cases occurred over the same period at 49.1 cases (95% CI 46.4-51.9) per month pre vaccination compared to 78.8 (95% CI 70.3-87.9) cases per month post vaccination ($p<0.001$). Myocarditis occurred within a median of 3.5 days of most recent vaccination (3.0-10.8 days) during the vaccination period. Median age of occurrence was 36 (26-48) years. Of the myocarditis cases observed after vaccination, 20% were observed after first vaccination and 80% after the second vaccination. Ninety-five percent of affected patients were admitted to the hospital, and all were discharged after 2 or 3 days. No deaths were observed but 35% of patients developing vaccine related myocarditis remained symptomatic after last follow up. Long term follow up of these patients has not yet been provided. However, economic consideration related to management of myocarditis and potential long term consequences will also need to be tracked and addressed. Pericarditis took longer for clinical presentation and increased from 40.5% occurrence after the first vaccination to 59.5% occurrence after the second vaccination. Median time of onset was 20 (6-41) days after most recent vaccination. The median age of occurrence was 59 (46-69) years. Only 35% of patients with new pericarditis were hospitalized and all were discharged. At last follow up, though, a higher proportion were still symptomatic [62% (95% CI 46-76)]. Again, long term follow up of these patients has not yet been provided. The majority of both myocarditis/pericarditis events occurred in males. Similar evidence of COVID-19 vaccination induced myocarditis/pericarditis has been observed by other investigators [12-18]. A notable and consistent observation is that there is a substantial increase in myocarditis/pericarditis occurrence from first vaccination compared to second vaccination and relevance of this to clinical effect of a boost (or likely third vaccination) is not well explored long term in young healthy adults. PLUS cardiac test (GD Biosciences, Inc, Irvine, CA) is a validated blood test of multiple circulating protein biomarkers used to predict 5 year risk of acute coronary syndrome in healthy adults related to cardiac endothelial cell damage [19]. One investigative group [20] measured PLUS score prior to COVID-19 pandemic to after COVID-19 vaccination in 566 young adults. PLUS scores within 2-10 weeks post second vaccination were compared to scores 3-5 months prior to vaccination. Risk of acute coronary syndrome increased from 11% (pre vaccination) to 25% (post vaccination). These results support that autoimmune

endothelial inflammation (part related to IL-16, soluble Fas elevation) may be involved with vaccine induced cardiac pathology [21, 22].

Cardiac Toxicity Related to Spike Protein

Mechanism of myocarditis and pericarditis appears related to vaccine mRNA expression of spike protein. COVID-19 vaccine produced spike protein binds to ACE2 located on endothelial cells of vascular vessels [23] and cardiac myocardium [24]. In vitro studies demonstrate that spike protein binding to ACE2 disrupts endothelial cell function and survival. One study [25] in Syrian hamsters demonstrated spike protein binding to ACE2 caused increased cellular mitochondrial fragmentation which led to endothelial cell dysfunction. Another study [26] showed that spike protein induced degradation of endothelial cell junctional proteins leading to disrupted endothelial barrier function. This was also felt to be contributing to endothelial damage by others [27]. The S1 subunit of spike protein leads to cytotoxic effect via binding to neutral phospholipid membranes [28]. It is unknown what long term cardiac damage is generated by vaccine expressed spike protein and immune reaction induced by each vaccination treatment, particularly with respect to cumulative adverse effects on myocardium, endothelium and other organs expressing ACE2 or involved in vaccine immune response damage. It must also be noted that spike protein expression from intramuscular vaccination is not limited to the injection site [29]. The expression product penetrates a variety of critical organs (brain, liver…) via systemic distribution [6, 30] and has been found in plasma of individuals post inoculation [29]. Furthermore, the lipid nanoparticle component (LNP) of BNT162b2 carries its own toxic associations. These include inflammatory reactions (related to PEG-2000 component) [31] and allergic events increased with repeat injections [32]. Relationship of systemic spike protein expression to added booster treatments over time have not been well evaluated.

Long Term Booster Vaccination Spike Protein Risks

There are a number of long term issues to consider regarding vaccine expressed spike protein and induced ACE2 signal activation in various body organs. First, it must be understood that the vaccine spike protein is a genetically modified protein and is not 100% wildtype protein structure. It is modified at positions 986 and 987 with proline residues on the S2 subunit [33]. This was done to enable better antibody access [34]. However, despite better antibody access and improved induction of neutralizing antibodies more non neutralizing autoantibodies are also produced to a variety of normal organ antigenic signals, including transglutaminase (tTG), myelin basic protein (mBP) and thyroid peroxidase (TPO) [35-38]. Assessment of long term disease occurrence related to induced autoantibodies is still too short but tTG antibodies have been associated with Celiac Disease, TPO with Hashimoto's thyroiditis and mBP with multiple sclerosis. Of concern with this observation is the potential risk of late developing autoimmune disorders. These would generally take several years for clinical syndromes to become evident [39] and could provide greater risk to a younger vaccination population, thereby justifying long term follow up, particularly in younger vaccination (or boost) participants. Each additional induction of spike protein through follow up vaccination would likely increase risk of autoimmune antibody production and may contribute to increasing chance of serious late developing autoimmune illness [38]. Several reports of early autoimmune thyroiditis have in fact already been noted post SARS-CoV-2 vaccination [40, 41]. This would also raise concerns in weighing risk:benefit of mass vaccination programs involving young healthy adults [37]. Spike protein may also impact directly micro vasculature of the brain and leydig cells of the testis via ACE2 binding potentially influencing later dementia onset [42] and reduced reproductive function [43-46]. Additionally, the GxxxG motif's contained in spike protein produced by vaccination are consistent with prion protein activity [47]. This has not been clinically verified as cause and effect, but it would seem prudent to track to determine relationship of potential late developing neurodegenerative disorders [37]. Several investigators in one controversial analysis [6] looked at risk:benefit of COVID-19 inoculation vs. COVID-19 infection by preforming a "best case scenario pseudo-cost-benefit analysis". Both a global analysis and an analysis with local clustering assessment was performed. The risk:benefit ratio of death in this analysis was calculated for the 65 and over age group. Unexpectedly, patients who were inoculated for COVID-19 in the 65 and over age group in the USA were 5 times more likely to die over a prolonged time period from vaccination (in the paper termed inoculation) toxic effect over death from COVID-19 infection and/or post infection treatment. Risk:benefit was predicted to be even worse with younger age groups. These

results are not conclusive but certainly suggest further need for assessment of overall survival between vaccinated/boost and non vaccinated/boost subjects. Studies related to retrospective insurance claims and overall prospective survival assessment comparing vaccinated, vaccinated and boost populations to pre vaccination periods or concurrently to those with natural infection and/or no vaccination are prudent.

Vaccination Limits with SARS-CoV-2 Variant Infection

COVID-19 vaccination efficacy is increasingly limited [48-50] by rapid SARS-CoV-2 variant spread [51-53], and wanning durability of antibody response [54-59]. These factors contribute to increasing SARS-CoV-2 variant strain breakthrough infection [60, 61] and provide evidence of "leaky vaccine" characteristics and lower immune activity against the Delta variant and other variants depending on position of spike protein mutations [55-59]. One solution is to provide boost vaccination to transiently improve antibody circulating levels. However, variant strains of COVID-19 continue to evolve and vaccination with the original SARS-CoV-2 (non mutated) spike protein increasingly offers less antibody protection [62-64]. Already further demonstration of ineffective neutralizing antibody against subsequent variants have been observed in addition to increased resistant SARS-CoV-2 variant infection [51, 55, 58, 60-62]. One example of limited benefit of vaccination was recently demonstrated in an outbreak of an early delta variant involving spread from one source to 42 people of which 39 were fully vaccinated. Fourteen of the 42 also developed severe infection [65]. Evidence by Riemersma et al in another study found no difference in viral loads comparing unvaccinated vs. vaccinated infected people and suggest that spread of virus from vaccinated people with infection is just as likely as from non vaccinated [66]. Moreover, Subramanian et al failed to show any benefit in occurrence of COVID-19 new cases related to percent of population who received full COVID-19 vaccinations [67]. They studied and compared 68 countries worldwide and 2,947 counties in the USA. Very surprisingly in review of the top 5 counties of fully vaccinated population (99.9-84.3%) in the USA, four were identified by the CDC as "high" (not "low") transmission counties. Three of these 4 were over 90% fully vaccinated. Additionally, in a study involving 2,225 cases of Omicron variant compared to 9,712 cases of Delta variant, secondary SARS-CoV-2 infection was 1.17 (95% CI 0.99-1.38) fold higher with Omicron compared to Delta in unvaccinated patients but was 3.66 (95% CI 2.65-5.05) fold higher in fully vaccinated plus boosted patients [68]. These results support suggestion of COVID-19 variant transmission not related to vaccination and support consideration of "learning to live with COVID-19" at this point given increasing limits in vaccination protection to new variants, similar to the approach taken with influenza back in 1918 which has been maintained for more than the last 100 years with justified acceptance.

Geographic expansion of the Mu variant [53] which contains an expanded string of spike protein mutations (T951, YY144-145TSN, R346K, E484K, N501Y, D614G, P681H and D950N) demonstrates resistance to vaccination induced antibodies [53]. Mu variant is however less infectious than Delta, but Lambda variant [69] demonstrates two mutations (T761, L452Q) which enhance infectivity and 3 spike protein mutations (RSYLTPGD246-253N, 260 L452Q, F490S) which also provide resistance to vaccine neutralizing antibody. Moreover, during the next year, further mutant attenuation to Delta variant could lead to other potential resistant variant strains [61, 70]. Omicron (B.1.1.529) is a good example of amplified resistance to COVID-19 vaccination related to spike protein mutations [71]. In total, greater than 30 mutations are observed with Omicron and 15 are contained within the receptor-binding domain of the neutralizing antibodies induced by current COVID-19 vaccination explaining reduced effectiveness. Liu et al [72] demonstrated marked reduced responsiveness to neutralization by serum from both SARS-CoV-2 convalescent serum and from serum of individuals fully vaccinated from serum of current COVID-19 vaccines including patients already fully boosted. However, pathogenicity appears significantly less with Omicron thereby justifying less need for vaccination and possibly supporting change in medical management from mass vaccination to enablement of less risky populations to have choice for natural infection induced immunity vs. requirement of booster vaccination. Further mutations related to mass vaccination with current "leaky" vaccine effect would be expected to continue to involve spike protein. Resistant strain enhancement is increased by multiplying vaccination with "leaky vaccines". Mass management with "leaky" vaccines could also risk mutations related to pathogenicity. An example of "leaky vaccine" consequences was recently highlighted in a study

involving whole genome sequencing of SARS-CoV-2 involving 1,373 patients with COVID-19 in San Francisco. Analysis was done from 02/01/2021 to 06/30/2021. Comparison of SARS-CoV-2 variant infection was explored between unvaccinated and vaccinated patients. Fully vaccinated patients were quite significantly shown to be more likely to be infected with variants carrying mutation associated with decreased antibody neutralization (78%) compared to unvaccinated patients (48%, $p<0.0000001$). Based on this analysis it was the vaccinated patients who carried and spread the majority of resistant variants [73] not participants with natural immunity following infection. There is justified concern that vaccination of the immune compromised population without sufficiently effective broad therapeutic measures to limit ongoing viral replication and address multiple variant breakthrough infection provides for conditions of inevitable ongoing resistant viral variant evolution [74, 75]. In one recent outbreak of symptomatic COVID-19 variant breakthrough infection, 74% (346 of 469) of patients who had previously received complete vaccination succumbed to Delta SARS-CoV-2 breakthrough infection [52].

Natural SARS-CoV-2 Immune Response

"Broad natural immune response" has been shown to be effective in recovered patients which conservatively now total close to 50 million in the United States [76-78]. Although recent estimates using comprehensive quantification and a database driven inference model involving county scale analysis in the USA, suggest more than 3 fold higher numbers of Americans have been infected with COVID-19 [79]. Such estimates are also likely higher with onset of Omicron. Cleveland Clinic recently published an analysis of 52,238 employees they were tracking to assess response to COVID-19 infection [80]. It was found that employees with no prior SARS-CoV-2 infection who got vaccinated did not show any added benefit over patients who had natural infection SARS-CoV-2 without vaccine. Remarkably, none of the 1,359 employees who had prior SARS-CoV-2 infection without vaccine developed recurrent SARS-CoV-2 infection in follow up. Another study assessing reinfection following natural [81] SARS-CoV-2 infection (PCR or antibody verified) involving 615,777 participants followed over 10 months also observed very low reinfection rate following SARS-CoV-2 infection and natural immunity (0-1.1%). Infection recurrence also surprisingly was not observed at increased rates over time suggesting durable protective immune response following natural infection. This was further supported by a 43,044 patient assessment which again identified a low (0.7%) reinfection rate following SARS-CoV-2 infection not related to vaccination [82]. There was also no evidence of waning immunity with over 7 months follow up [82]. Most recently another assessment of repeat COVID-19 infection was shown to be 80 to 100% reduced in patients with prior SARS-CoV-2 infection [83]. Other work showed vaccination with BNT162b2 had almost 6 fold increase risk of breakthrough infection and over 7 fold increased risk of symptomatic disease compared to people not vaccinated but with natural immunity [84]. The importance of these observations in comparison to COVID-19 vaccination is that they provide evidence of support to consideration of not requiring booster vaccination particularly in environments where variant COVID-19 (i.e., Delta, Omicron) is likely.

Severe morbidity/mortality in the younger adult age group with COVID-19 recurrence is close to zero, however toxic outcomes, both short term and long term, to the vaccine (or boost) are observed at increasing rates as dosing is multiplied with the boost (and "more boost") strategy. Recent analysis of 32,430 matched patients randomly identified from a pool of 104,932 patients from the Maccabi Healthcare Services centralized computerized database [84] investigated patients of age 16 years and older who had either natural COVID-19 infection (no vaccination) or vaccination (BioNTech/Pfizer vaccine) with no prior COVID-19 infection. Follow up period was from 06/01/2021 to 08/14/2021 when Delta variant was identified as the active variant in the region of patient inclusion. COVID-19 infection was verified by CDC guidelines. Results revealed a 13 (95% CI 8-21) fold higher risk of breakthrough infection (1.47% vs. 0.12%, $p<0.001$), 27 (95% CI 13-58) fold higher risk of symptomatic infection (1.18% vs. 0.049%, $p<0.001$), and suggested an 8 fold higher risk (0.05% vs. 0.006%) of hospitalization in the patients with BioNTech/Pfizer vaccination as opposed to natural infection and no vaccination. This analysis was consistent with other analysis [76, 84-86] in demonstrating that natural immunity over vaccination provides possibly stronger protection against SARS-CoV-2 infection including against Delta variant.

So why would natural infection provide any possible benefit over vaccination? It's been shown that spike protein antibodies using nucleic acid amplification test and serologic assays achieve much higher circulating levels following vaccination than spike protein antibodies with RT-PCR confirmed natural infection [87]. However, the durable broad based activity from natural infection against multiple SARS-CoV-2 protein antigen targets, particularly highly conserved nucleocapsid protein, is thought by many to be more effective in pandemic management [88, 89]. Alfego et al [87] demonstrated that 90% of 39,086 patients with natural infection had significant elevation of neutralizing antibodies to SARS-CoV-2 21 days after infection. Surprisingly, 88% (95% CI 86-89%) maintained neutralizing antibody to spike protein 300 days post infection. This was higher in those under 65 years old compared to those 65 years and older [89]. Others also found similar durable broad neutralizing antibody response to multiple targets following natural SARS-CoV-2 infection further supportive of robust protection following natural COVID-19 infection [90]. As previously described, natural immunity results in broad antibody response which also involves well conserved viral targets (i.e., nucleocapsid protein [91]) that will minimize risk of "leakiness". Highly conserved targets are more critical for SARS-CoV-2 survival and when mutated are less prone to generating surviving viral species. A study by Wang et al involving sequential neutralizing antibody assessment in 63 patients at 1.3, 6.2 and 12 months after natural infection tracked memory B cell response. Results showed durable memory B cell activity at 1 year follow up. Moreover, neutralizing antibody activity was also assessed against various variant strains and was shown to be of similar or greater neutralizing activity as compared to the activity against the original Wuhan Hu-1 strain following vaccination of naïve individuals [88]. Neutralizing antibody following natural infection involves the mutated variant virus sequences whereas the "neutralizing" antibody from mandated vaccines is limited to the spike protein sequence of the original COVID-19 virus. The mandated vaccine neutralizing antibody has not changed and does not adapt to the new COVID-19 variant mutations. It appears that natural immunity provides a durable, adaptable and broad based capability related to more than just antibody response. The broad long lasting immunity from natural infection of SARS-CoV-2 may explain the observation by Subramanian et al [67] following testing in 68 countries and 2947 USA counties in which fully vaccinated participants did not show any reduction in new COVID-19 cases compared to non vaccinated participants many of whom had prior natural infection.

Inconsistent Antibody Response

High antibody response is rarely associated with natural SARS-CoV-2 infection recovery. Antibody titers in natural SARS-CoV-2 infection are observed to be low or zero in patients with less severe disease [92-94] supporting that effective immune clearance of SARS-CoV-2 and/or variants is not exclusively dependent on high antibody titers. This was consistent with SARS-CoV-1 infection which revealed strong T cell memory response but short lived B cell antibody response after infection [95, 96]. However, high antibody titers were seen in others but in many of those correlation was shown with detrimental clinical effect with SARS-CoV-1 [97, 98]. Increased mortality and severity of infection has been shown in some reports involving COVID-19 patients to be related to increased (not decreased) antibody titers [92, 99, 100]. These same results had been previously demonstrated in animal models [101-104]. Also, inactivated whole virus and whole viral based vaccines for SARS-CoV-1 or MERS-CoV resulted in identification of antibody dependent enhancement (ADE) related immune pathology [98, 105-107]. Similar effect has also been demonstrated with F/PV type II coronavirus, coronavirus 229E, dengue virus and other viruses [108-111]. These observations support possibility of ADE contributing to SARS-CoV-2 vaccination toxic effect over long term and add to the risk and economic consideration of additional booster vaccinations for young healthy adults. On the other hand, not all patients who recover from natural COVID-19 infection have detectable antibodies, strongly suggesting effective reliance of SARS-CoV-2 clearance towards other (non antibody related) immune mechanisms [112]. SARS-CoV-2 antibody response in newly infected hospitalized patients (n=173) in another report [113] demonstrates <40% of total antibody induction within 7 days of infection. However, SARS-CoV-2 viral RNA was more rapidly decreased by 66.7% within 7 days, thereby further suggesting effective broad natural immune mechanisms independent of antibody response are involved in SARS-CoV-2 clearance.

Cellular Immune Response

Closer review of immune response in COVID-19 infection reveals that CD8+ levels consistently

correlate with COVID-19 disease severity [54] and non-hospitalized patients who have successful recovery from COVID-19 have robust evidence of increased SARS-CoV-2 memory CD8+ T cell detection. These results support cellular immune mechanisms of SARS-CoV-2 clearance related to CD8+ T cell involvement [114]. T cell immunity has been shown to protect against rechallenge of SARS-CoV-2 in rhesus macaques [115]. As mentioned, reinfection of SARS-CoV-2 in patients recovering from first natural infection (without vaccination) is infrequent [48]. SARS-CoV-2 specific T cells, in fact, have been identified in patients following infection [112, 116]. Patients with severe COVID-19 infection have been shown to have very low CD8+ T cell function and count [49]. Others have also seen similar results [117, 118]. Memory T cell response following SARS-CoV-1 and SARS-CoV-2 has been shown to be of prolonged duration in patients following natural infection [96, 119, 120]. Presence of memory T cells have also been shown to protect from lethal rechallenge of COVID-19 in animal models [95]. Moreover, memory T cell response has been shown to be robust in non symptomatic infection and low in patients with severe symptomatic COVID-19 [49]. The correlation of increased memory T cell response and positive clinical response was particularly strong in patients with minimal circulating SARS-CoV-2 antibodies [49]. Similar correlated memory T cell response to clinical benefit has been observed with other viral pathogens [49, 121-124]. Memory T cell response involving patients who have not demonstrated recurrent infection with SARS-CoV-1 have demonstrated durable activity for many years [96, 119, 120]. Further clinical studies with MERS-CoV and SARS-CoV-1 also reveal protective effect in patients with no detectable antibody response [95, 125-127]. In these latter reports, the protecting durable T cell response was also demonstrated for many years. In summary, elevated T cell response particularly involving CD8+ T cells and memory T cells, as what is observed in natural SARS-CoV-2 infection, have consistently shown prolonged protective effect against further disease recurrence and severity.

Experimental Cellular Response Therapeutics

In the event that symptomatic infection progresses, there remains a limit to validated anti COVID-19 therapeutics. FDA indicated immunotherapeutic intervention Remdesivir [128] if necessary in symptomatic young healthy adults is one of a small number of therapeutic management options cleared by FDA. Another therapeutic recently receiving FDA emergency use authorization is Ritonavir (PF-07321332) which was found to reduce risk of hospitalization or death compared to placebo in high risk adults (www.FDA.gov). Other therapeutics outlined by McCullough et al [129] review unvalidated management that has worked in some but remains controversial without FDA randomized trial validation. Vaccines are not designed for therapeutic management so until more therapeutic approaches are approved, patients developing severe infection have limited validated options.

Therapeutics enhancing cellular immune response against multiple SARS-CoV-2 survival mechanisms may be of valuable research consideration and establish a novel platform which would be additive to potential future combination therapy management with Remdesivir and/or Ritonavir. GMCSF, for instance, enhances long term cellular immune response against a variety of pandemic viral species. Several murine model studies have demonstrated decreased morbidity and survival benefit to single agent GMCSF with endemic viral pathogens [130]. GMCSF also induces protection against lung cellular inflammatory damage related to SARS-CoV-2. There is extensive evidence of GMCSF effects to enhance alveolar cell activity, CD8+ T cell response and humeral immune response [131-134]. With early influenza virus (IV) and SARS-CoV-2 infection AEC's release GMCSF for protection leading to prevention of capillary leakage and immune enhancement against invading virus. GMCSF drives immune function of alveolar macrophages and improves epithelial repair processes [135]. This early use and/or enhancement of immune function and alveolar protection with elevated GMCSF expression has demonstrated preclinical and clinical benefit. Using a nebulizer administration [136] recombinant GMCSF demonstrated clinical benefit in a small number of patients with viral related acute respiratory distress syndrome (ARDS) [136, 137]. A study in Belgium is currently testing Leukine (rhGMCSF) via nebulizer in COVID-19. Immune function enhancement has been shown in rhGMCSF treated patients compared to non-treated ARDS patients consistent with preclinical evidence [132]. GMCSF treated patients demonstrated alveolar cell protection, enhanced alveolar cell activity and shift to activated macrophage killing response. These results support the beneficial therapeutic effectiveness of GMCSF expression even in later stages of pulmonary viral infection complicated by ARDS. Safe administration of rhGMCSF via inhalation therapy in 19 patients

with autoimmune pulmonary alveolar proteinosis was also demonstrated to show benefit [138]. Elevated IL-17 in bronchial alveolar lavage fluid correlated with GMCSF induced cytokine biomarker associated with benefit.

Another platform direction involves downregulation of furin endoprotease which cripples SARS-CoV-2 cellular entry, protein assembly and cellular egress [139, 140]. Furin is responsible for S1/S2 "cleavage activation" and membrane fusion including S2 subunit and S2' cleavage site following SARS-CoV-2 spike (S) glycoprotein RBD:ACE2 interface [141]. There is a concentration dependent effect of furin inhibition on infectivity of MHV-A59 CoV and on infectivity and cell to cell fusion of MERS-CoV [142]. In addition to coronavirus, evidence supporting furin antiviral activity is demonstrated extensively in HIV, influenza (including H7N1), flavivirus, pneumovirus and several other viral species *in vitro* and *in vivo* without evidence of significant toxic effect [143-145]. Nelfinavir, a protease inhibitor used to treat HIV has shown the ability to inhibit furin and is being repurposed in clinical trial involving SARS-CoV-2 [146, 147]. Evidence also suggests combination with Cepharanthine, an anti-inflammatory drug, further improved response via inhibition of SARS-CoV-2 binding to target cells [148].

Vigil Plasmid (VP) is a cGMP product designed to concurrently express GMCSF and knockdown furin (bi-shRNA^{furin} DNA) [149]. Vigil immunotherapy, a processed autologous tumor tissue transfected with VP, which is a cancer directed product that has gone through extensive clinical evaluation with a favorable tolerability profile and significant anticancer activity resulting in relapse free survival and overall survival benefit [150, 151]. Given safety and extensive evidence of efficacy in oncology patients, it has been conceived to repurpose VP to address treatment of SARS-CoV-2. VP potentially may provide several separate mechanisms of anti SARS-CoV-2 activity related to combination of GMCSF expression and furin knockdown.

Measurable T cell Memory Response

Following infection with SARS-CoV-2, the SARS-CoV-2 antibody expression can be transient, however T cell memory is more reliably detectable for more than 1 year suggesting advantage in cellular response to clearance of SARS-CoV-2 and supporting value as a measurable biomarker of protective natural immunity [96, 119, 120]. Unfortunately, accurate circulating T cell memory determination following COVID-19 infection has been difficult to achieve, largely related to high false positive results related to T cell cross-reactivity from non SARS-CoV-2 seasonal coronavirus antigens (i.e., coronavirus strains 229E, NL63, OC43, HKU1) [152]. However, recently Lehmann et al [153] demonstrated with new established immune response criteria elimination of false positive results. His team verified accurate T cell memory activity in clinical testing. Four criteria were established to define SARS-CoV-2 memory T cell presence. One, detection of ex vivo IFNγ producing effector memory T cells was defined. Two, negative controls of mega peptide pools were utilized. Three, T cell response scores based on affinity to test peptides was established. And four, a multi-antigen-specific T cell response profile was established. Determination of circulating T cell memory capacity in patients following SARS-CoV-2 infection particularly asymptomatic or minimally symptomatic infection observed with Omicron will be important to provide objective criteria defining broad established natural immunity. It has been demonstrated that multiple compartments of circulating immune memory fractions (CD4, CD8 cells) can be defined against SARS-CoV-2 within 8 months of infections [154]. Development of natural immunity which demonstrates more prolonged and durable protection against breakthrough infection may be more effective in control of variant disease exposure. Further effort of cellular immune activating therapeutic approaches in combination with quantitative assessment of T cell memory response may expand to a more effective herd immunity. As such testing is validated and expanded, future opportunity will include measurement of T cell memory against SARS-CoV-2 and variants and other biomarkers as guidance to management based on immune status, risk of morbidity/mortality and choice of medical management rather than broad whole population mandates and economic shutdowns.

CONCLUSION

In conclusion, numerous toxic activities occasionally leading to hospitalization and prolonged debilitation or even death from multiple COVID-19 vaccination and boost induced causes in addition to increasing risk of breakthrough infection and shedding of virus to other vaccinated or non vaccinated subjects, raise doubts of risk:benefit ratio in the young healthy adult population where health risk from natural SARS-CoV-2 infection is

minimal. More experience, long term follow up and additional studies are still required but at this point in time our conclusions to questions posed are as follows. Based on our assessment 1) elderly and those with immune compromise and/or medical risk generally benefit from COVID-19 vaccination and boost, however young healthy adults would be optimally served through choice of management (vaccination/boost or natural infection with therapeutic support). 2) Vaccination/boost persistence to spike protein variants has a high proportion of breakthrough infection and will be increasingly limited in capacity to halt a late COVID-19 variant pandemic. Moreover, greater risk of further variant occurrence may compound current "leaky" vaccination/boost strategy. 3) Natural infection of recovering young healthy adults will support herd immunity in combination with vaccination/boost of greater risk populations. Young adults should be offered a choice and not vilified for optioning to the risk of fulfilling heard immunity with natural infection. 4) Therapeutics development is critical for management of vaccinated/boosted subject's breakthrough infection and those with advancing natural infection. Comparison between mortality and complication rates in all age groups between vaccinated and nonvaccinated patients is necessary to address the role of vaccination and nonvaccination effect.

These results suggest reduced advantage for COVID-19 boost over natural immunity and justify choice for young healthy adults with their physician in decision of boost or no boost. Furthermore, Omicron, being a less pathogenic coronavirus, may be a solution not the problem to our pandemic. A base level of herd immunity against future coronavirus infection may need to be established to multiple spike protein mutations not to prevent further epidemics but to minimize pathogenicity similar to what is observed with the influenza management. However, diligence and education with peer reviewed literature support towards prevention for high risk subpopulations will be increasingly required for future medical management involving both development of new vaccines and therapeutics against COVID-19.

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