It has been 11 months since I first posted thoughts about the COVID-19 pandemic on the AIT Strategies website. I will leave my string of comments posted for posterity as this crisis continues to evolve. They are worth revisiting from the bottom of this web page forward. We now have a vaccine roll out in progress and the pandemic will likely be contained. The ability of the virus to mutate and adapt will always be a threat, but if there is little virus out there in the community, the likelihood of a mutation that escapes the vaccines control will be low. Therefore, continuing to practice social distancing is important until the community prevalence drops substantially.

As a clinical immunologist, my perspective of disease is different from that of many medical specialists. I look at this disease from the perspective of host defense rather than the viral toxicity. Adverse outcomes to acute infection are not the usual progression except in select patients who generate a dysregulated immune response.

I have advocated for a model of prospective comparative trial design intended to rapidly assess miscellaneous widely available treatments that plausibly might prevent an acute infection from causing severe disease, not through anti-viral activity, but by shifting the character of induced immunity in the infected host patient. I have argued that although subtle effects will likely be missed in such a research model, signals that are substantial in either aggravating or preventing progression to severe disease will be detected, and if a signal is replicated in a repeated small rapid demonstration; then confidence in the observation should be high. Data driven findings could then drive policy decisions, further study confirmations and implementation of clinical interventions. A process based on sound rather than anecdotal preliminary observation.

The emphasis in such a *CAISS* (Community Actionable Intervention Screening Study) model is simplicity of design, simplicity of data collection, but features built in process for iterative modification, and with a reserved potential to drill deep to chase important signals. The concept should be performable in a community setting with minimal administrative burden to front-line clinics. *Unfortunately,* this is not a model that exists for practical purposes in modern western medicine.

Standard research protocols appropriately are subject to rigid scrutiny at multiple levels and complying with the governing regulations is difficult and requires dedicated personnel both within clinics and within institutional administrations. Costs are substantial and most caregivers cannot easily participate.

In the face of acute pandemic, it would be possible to run rapid CAISS models, but when active disease fades ability to accrue such a study model disappears. I do not believe a CAISS model will be implemented in the context of COVID-19 in time to significantly alter the trajectory of the current public health crisis; however, there is preliminary evidence that some counter-intuitive interventions may impact likelihood of disease progression in Covid-19. As part of the review of the entire pandemic and the body of information that is gathered of coming months, I believe the evidence will point

to the plausibility of actionable interventions potentially being able to modify the likelihood of progression to severe disease. As part of a program for pandemic preparedness in the future, I strongly recommend that a model of CAISS be established by regulation that would only be operative in declared national public health emergencies. The regulation would provide for a clinic participation in a CAISS program using a central institutional and ethics oversight model that relies on simplified central data collection and minimal demands on the front-line clinics. The CAISS model is dynamic and incorporates iterative research assessment as part of an ongoing process in parallel treatment cohorts. The central oversight can adjust the treatment regimen or substitute for clearly ineffective or adverse regimens according to a pre-specified algorithm. Detection of signals and replicated confirmation could occur rapidly in such a model. The potential to convert a lethal pandemic to much less harmful epidemic would be the objective.

If an infection can spread in a population but it carries no toxicity it is not a pathogen. If an organism is too toxic, it is unlikely to spread uncontrolled. However, a disease such as Covid, that generally produces mild disease and is very contagious but only in a minority of cases induces lethality is a formula for a pathogen profile that most likely will be repeated in future pandemics. With Covid-19, unprecedently rapid vaccine development using the latest tools of molecular biology appears destined to control this event. However, success of vaccine projects is never assured *a priori*. In the absence of a vaccine, an actionable intervention that modifies the severity of the extreme cases might be the necessary solution. In one year, we have had 500,000 Covid deaths in the US alone and untoward economic damage across the society. If a CAISS model had been implemented last Spring and an actionable intervention identified rapidly, the epidemic spread would have continued, but the death toll and the economic consequence might have been vastly different.

The obstacle is one of convention and the clinical research& development process. That should not be challenged and local institutional controls should be the norm, however in times of national public health emergency, flexible prospective study design with central oversight and community participation that focus on community outcomes should be implemented to identify plausible disease ameliorating interventions. The ability to harness creative solutions rapidly would thus be enhanced. I strongly recommend this to policy makers that will be reviewing Covid 19 and its handling over the coming months.