



## Commentry

# Immunological Defence beyond Vaccination – A Review

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Received: 16 September, 2020

Accepted: 28 September, 2020

Published: 29 September, 2020

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## Introduction

The Pandemic has been with us in the whole world for over half a year. There seems no signs of slowing down. Traditionally, infection problems are dealt with by experts and scholars who clarify the cause of the disease and the pathological involvements; work out the effective treatment protocol, then organize a public health program for prevention. Unfortunately, with regard to this current devastating pandemic, up to today there is yet no consensus on the use of therapy: anti-flu, anti HIV, antimalarials and steroidal classics have all been tried. New drugs, of course, has been on the list. The controversial views of the clinical scientists have invited the ambitious involvement of aggressive politicians who accordingly make their wise or stupid comments ruthlessly. With regard to the clinical involvements: those chronically ill and elderlies are expected to be more vulnerable. Nevertheless, with further development of the Pandemic, a much broader age range, from neonates, children to young and health, could all be victims. [1].

None of us could have experienced the 1918 Influenza Pandemic, which lasted more than two years; with 18 months of disastrous disturbances followed by scattered events extending to 1920 [2]. In the decades that followed, influenza epidemics on smaller scales have been common in the US and Asia, particularly China. Such epidemics lasted a few months, then disappeared.

Seventeen years ago, the Hong Kong experience of SARS has remained in the vivid memory of Hong Kong People. It gave us just over 100 dark days of threatening uncertainty, then disappeared totally within half a year.

If we compare today's Pandemic with the worst period of the 1918 Pandemic, it might seem that the present experience is worse. The universally shared feeling of today is therefore fear: fear among the medical professions, fear of health providers that facilities are drying up, fear from governments and economists that recession would be unpredictable. When is the Pandemic going to end?

A hopeful voice has been crying out louder and louder since there is a need to dilute the despair. The Vaccine is coming! There are over 100 institutes and pharmaceuticals toiling for vaccine production day and night. Countries including China announced that their vaccines have passed the safety requirements and dosage tests, and are ready for clinical trials. Some countries already signed contracts with producers for the exclusive provision of the successful vaccine. China vowed that their production could be for the whole world. The announcements do have soothing effects against worries and fears. Apparently, the current hope for the control of the pandemic, lies in the Vaccine [3].

Indeed, vaccines have solved a lot of problems related to infections. Varicella vaccine has eliminated small pox. Children from birth to two years all receive vaccines for measles, tetanus, whooping cough and pertussis which have freed them from those infections ever since. The most remarkable example is the orally taken, polio-vaccine which eliminated polio from earth [4]!

All these successful vaccines convince us that vaccine is the real hope for infections. Nevertheless, if we are aware of the sad examples, we might not be so optimistic. HIV infection experts have tried for some forty years, no vaccine is yet

available. Influenza vaccine which is so familiar to us, has changing efficacy ranging from 30–50% or lower. Tuberculosis has enjoyed generations of vaccine and yet after 70 years, has not reached the efficacy expected. More desperate examples include parasitic infections like malaria, schistosomiasis etc, which are “vaccine resistant” [5].

Now that we feel excited to know that many vaccine manufacture groups have passed safety and dosage tests, can we jump to the conclusion that the successes would solve our problem?.

### Effective vaccine

As a matter of fact, the standard requirements of an effective vaccine to control an infection has long been documented [5]. The following table gives a brief summary.

Features of effective vaccines	
Safe	Vaccine must not itself cause illness or death
Protective	Vaccine must protect against illness resulting from exposure to live pathogen
Gives sustained protection	Protection against illness must last for several years
Induces neutralizing antibody	Some pathogens (such as poliovirus) infect cells that cannot be replaced (e.g., neurons). Neutralizing antibody is essential to prevent infection of such cells
Induces protective T cells	Some pathogens, particularly intracellular, are more effectively dealt with by cell-mediated responses
Practical considerations	Low cost-per-dose Biological stability Ease of administration Few side-effects

We could follow the logic and workout useful ideas:

- i. The vaccine must be proven safe i.e. not imposing any pathological harm, immediately after the vaccination and later in the subsequent months. Short term safety refers to three months and longer term could extend to more than 6–9 months, and some vaccines in the past have serious adverse effects after even longer periods.
- ii. The vaccine is meant for a specific target organism i.e. COVID-19, and the immunological achievement must be related to COVID-19 control, not general response.
- iii. The vaccine must provide long-term protection, not “one shot effect”.
- iv. In response to the vaccine, the recipient must be proven to develop antibodies specific to COVID-19.
- v. The vaccination should result in the promotion of favourable cellular and serological responses (T cells related) for sustained effects.
- vi. The mode of administration: injections, inhalation or oral would be important practical considerations.

By now we should understand that our COVID-19 vaccine has many hurdles to go through in the subsequent months [6,7].

So far our discussion has been focused on the target orientated way of immunological defense against the invading COVID-19, i.e. the vaccine, which once proven successful, will provide quick and effective prevention against COVID-19.

### Innate defence

Actually, our immune system is responsible to combat invading organisms, and under normal circumstances, without unusual virulent invasions, the system works well, without the need of any vaccine. It is this general immunological strength of infection resistance that keeps us away from being infected. The whole family could succumb to the COVID-19 infection when all the members have deficient immunological strength. On the other hand, it is not uncommon to find one or a few of the family members staying healthy in spite of others contracting the infection. The healthy members must have more efficient immunological strength. This extra defense strength is innate with the healthy member, not related to any vaccine.

### Trained immunity

“Trained Immunity” offers Protection against infection beyond vaccines.

Host defense against infection depends on the reactions of its immune system. The primary response is taken care of by the Innate Cells which rapidly recognize the invading pathogens and start eliminating them through phagocytosis and initiating chain reactions in the process of activating the adaptive immune system. It has been assumed that immunological memory is an exclusive hallmark of adaptive immune responses.

Recently, it has been found that innate immune responses could be enhanced and sustained following initial exposure to infectious pathogens, resulting in immunological memory which helps to protect against re-infection [8]. Experimental evidences were collected in animal platforms of candida albicans infection [9]. Clinically, observations related to general resistance to infections after early life vaccinations against TB, measles, Polio and others have been made and studied and sustained immunological defense was observed. Netea’s research group in the Netherlands suggested the term “Trained Immunity” to signify this phenomenon [10].

Netea’s group issued a most revealing manuscript in the “Cell” in May 2020 entitled “Trained Immunity”: a tool for reducing susceptibility to, and the severity of SARS-COV-2 Infection” [11]. They argued that since COVID-19 infection is usually mild and only a small proportion of patients develop into pneumonia, it might already indicate that the majority has sufficient trained immunity to resist the SARS COVID-19 virus. The more frequent succumb of the elderlies and patients with co-morbidities further illustrates that the trained immunity of these vulnerable groups needs boosting. They advocate the use of whole-microorganism vaccines like BCG, polio and measles as boosting agents to strengthen the trained immunity [12].

Can this innate immunological defense viz. “Trained Immunity” be stimulated and strengthened with simple therapeutic means? [12].

Documented reports about desirable ways of boosting innate immunological defence are plentiful, particularly in areas of laboratory research. Imagine an organism starting its attack on the respiratory system: first reaching the mucosa of the respiratory tract. Before penetrating through, it is met with the secretions present outside the cells. There are means to increase the secretion which contains defensive molecules to interfere with the organism's invasion. When the organism starts or succeeds penetrating, it meets a variety of T cells which defend either through direct attack or changing the immediate environment to a state unfavourable for the survival of the invading organism. Such sequential activities in fact are normal events for every human being. Common infections are resisted through effective mechanism as described. If those normal defensive activities do not work, the human race could not have been sustained. The "Herd Immunological Defense" theory as a way to control a rapidly spreading epidemic – allow the vulnerable to get infected widely, so that those with extra immune-defensive strength would help stabilizing the spread – might rely on the same argument.

### Beyond vaccination

Allopathic therapy today relies heavily (nearly solely) on target orientated treatment. General supportive measures tend to be ignored. Vaccine is a "bullet shot", created against a specific pathogen. Other boosting manoeuvres supporting the existing innate immune-defence ability is considered unimportant.

In 2017 and 2019, before the Pandemic started, Harvard scholars brought to the medical public an important message: that Vitamin D could be recommended for the prevention of respiratory tract infection. They produced clinical and public health data, together with laboratory research confirmations. Cold, humid Northern countries in the world do have more respiratory infections in Winter and Spring time when sunlight which helps the natural production of Vitamin D is deficient. Laboratory studies have worked out the molecular details how Vitamin D helps the immunological defense with essential supportive [13].

This message from Harvard gave us a lot of encouragement. It supports the holistic approach of boosting immunological defense. Sadly, when the COVID-19 started its attack in US, all attention shifted to target treatment, and currently, Vaccine.

### Traditional chinese medicine and immuno-defense

Traditional Chinese Medicine advocates holistic balance and harmonization for all therapeutic designs. Treatment could have some specific target, yet in the treatment protocol, a balanced support to all functional organs is advocated. Using the current language of Immunology, the balanced harmony could be an immunological state of neither over-activity nor underactivity.

Indeed, over-activity leads to allergy and autoimmune diseases while underactivity undermines normal physiological functions and invites pathological changes.

In the last two decades when scholars tried to supplement modern medical practice with traditional therapeutic options, the simple but logical immunological line of thinking has much been adopted.

We have explored, with the partnership of the Memorial Sloan Kettering Cancer Center of New York, medicinal plants that could immunologically counteract Cancer growth. We found five favorable herbs that deserved further explorations. Then we worked with Paediatricians on medicinal herbs that support treatment of allergic dermatitis and nasal sinusitis, using immunological platforms. The research is being continued.

Seventeen years ago, the Hong Kong SARS crisis gave us an opportunity to engage in viral infection prevention. While hospitals in China commonly used a large variety of herbal formulae together with modern drugs for the treatment of hospitalized patients, we believed that using simple herbal combinations for the protection of people at risk of disease contraction would be as important. Those are the hospital workers, relatives and friends of the infected, who need prevention. We created a herbal formula, not for treatment, but for prevention: i.e. for the boosting of natural immunological defence against SARS [14]. The idea was very much in line with the current "trained immunity" concept.

The formula consisted of two parts: part one was supportive of "Qi" and part two was a simple herbal combination advocated for mild symptoms (which to our mind, meant prevention of progress) "Qi" was an important ancient concept of balance and harmony which we took as prevention of deficiency in immunological defense.

During the climax of the SARS epidemic, hospital workers were under extreme stress because of the high risk of infection. We organized a clinical trial using the innovative herbal formula for two weeks. Over 2,000 volunteers participated. Subsequent, analysis showed 0 infection rate, compared with a 0.4% infection among those not taking the formula [14].

The convincing results gave us a lot of encouragement to continue research on the Preventive Aspect of the herbal products we used.

### Conclusion

Since the COVID-19 pandemic, reports from China again strongly recommended the use of complicated classical herbal formulae for hospital treatment. The overwhelming importance of hospital treatment has again diluted the importance of prevention. Moreover, the role of prevention is totally given to the hopeful vaccines. This might be a suitable time, for the standard commonplace aspects of immunological innate defence be seriously studied and be included into the immediate future planning, not only for COVID-19 prevention but also for other respiratory infections. Even when the effective vaccine becomes a reality, those at risk of infection with or without the vaccination could still benefit. Accordingly, we have worked out research protocols for the research pursue in a number of published manuscripts [15-19].

It has already been hypothesized that induction of trained immunity in general, and by BCG vaccination in particular, might be a potent preventive measure against COVID-19 infection, and / or might reduce disease severity. Several preliminary trials assessing the efficacy of BCG vaccination among healthcare workers have been started in the Netherlands and Australia, while preparation for similar trials are also active in a number of countries. Early results are expected towards the end of this year [11,20].

Assuming that commonplace, conventional anti-infection vaccinations and therapeutic measures using herbal medicine do have a common aim of boosting the trained immunity, now that COVID-19 vaccination trials have started, equivalent research efforts could be expected on herbal therapeutic measures.

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