

## **Covid-19 and the law of unintended Consequences. Should we account for immunity circannual rhythms, immunosenescence, vaccine based immunity imprint and vaccine interference in context of Covid-19 infection ?**

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As you may have noticed there are studies one of which was performed by the US Army presenting higher susceptibility to human coronavirus infections in people who underwent seasonal flu vaccination (1,2,3). There is even indication that susceptibility to Covid-19 infection is connected to the type of flu vaccine (4). The more over flu vaccination is proved to increase flu virus shedding in vaccinated symptomatic patients (5).

Immune imprint induced by early vaccination is another factor to be reported to effect responsiveness of the immune system to infections later in life due to its immunomodulating effect (6,7).

In line with the early effects of vaccination is the fact that cell composition of immune system can change substantially early in life due to environmental stimuli. Critical period in development of adult like B, NK and DCs populations was identified during the first 3 months of human life. Drivers of these changes are environmental stimuli (8).

Correction for time of BCG vaccinations should be taken in account when evaluating possible beneficial effects in Covid-19 pandemics (9).

It's of note that Flu and Covid-19 are not only air borne but they utilize the same receptor ACE2 to enter human cells (10). Reports indicating cross effects among flu vaccination and Covid-19 should be considered during the process of anti Covid-19 vaccine preparation and application.

The more over there is no way to exclude bidirectional effects among future Covid-19 vaccination and flu.

Possible protective effect of BCG vaccination is proposed and investigated.

We are under the risk that positive development during summer can lead us to the same positive expectation for winter season. It's of note that the same positive expectation was thought to be applied for winter season during the summer in 1918 flu pandemics (11).

Seasonality in immune system functioning (11) as well as susceptibility of Covid-19 to seasonal environmental changes (12,13) seems to be undervalued at the moment.

Enveloped viruses despite non enveloped viruses present seasonality with favor for lower temperature season (14).

Ordered phase of lipids in viral envelope increases with decreasing temperature in influenza virus. This process is thought to contribute to viral stability at lower temperatures (15).

Higher transmission rate under cold and dry environmental conditions was demonstrated in influenza virus in guinea pigs (16).

Seasonality of HCoV was investigated in Michigan households. Sharp seasonality with little spread after May until November or December was found. At the same time there was indicated likely low cross reactivity among different human coronaviruses and production of only relative immunity (17).

It's of note that some circannual rhythms are photoperiodic independent (18,19).

Due to the seasonality of immune system functioning and changes susceptibility of Covid-19 to environmental changes studies dealing with therapy or course of Covid-19 infection should deal separately with two seasons:

the winter season - October, November to April the summer season - May to September, October.

The effect of immunosenescence that imparts non specific and cellular immunity response in humans is

not reflected adequately in nowadays research (20) as well.

The last point to be stressed is underinvestigating protective and adverse effects in Covid-19 infection in highly exposed population. Such a population can include people sharing the same households with positively tested Covid-19 patients since it's known that not all people must be affected as illustrated by patient one in France. "He was sick for 15 days and infected his two children, but not his wife, who works in a supermarket," he said. (21)

Studies performed in highly exposed population could potentially help to navigate future research in investigation protective and adverse conditions for Covid-19 infections among other the effects of sex, ethnic group, age, social stress, vaccination status, medication and seasonality.

Unfortunately secrecy in excess to Covid-19 data gathered by governments (22, 23) and overload of bureaucracy disrupts attempts to performe such studies.

At the same time much more effort should be put in investigating the effect of cheap potentially effective therapies that could be used on mass scale like the use of intravenous high dose vitamin C in prevention of cytokine storm (24), it's immunomodulative and lung protective effects (24,25,26,27). The use of antimalarics (28,29) on it's own or in combination with macrolides and vitamic C, the effect of vitamin D (30), vitamins group B.

Disruption of Covid-19 envelope development by fenofibrate leading to impairment of viral replication was demonstrated in human lung cell cultures and is about to undergo clinical trials (31).

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