<u>Note 5. Why natural immunity and vaccines work together – Many locks vs. Single lock. Industry will always be slower than live biology.</u>

Everyone knows and understands that vaccines can block viruses and prevent many infectious diseases. They help the immune system, which is our biggest protecting organ. There are different ways of fighting viruses with our immune system: vaccination, monoclonal antibody therapy, natural immunity (also called 'Herd immunity').

<u>Vaccination</u> is an efficient tool for *preventing* viral diseases. It is based on using viral components, stripped of their infectious power (e.g. parts of viral particles, damaged viruses, etc.), in order to stimulate an immune response, which will remain in its memory. At later times (even years later) when coming in contact with the actual disease-causing virus, our immune system already has at its disposal (in its memory) tailor-made antibodies to fight it. This is called *active immunity* and works in a lock-key principle: our immune system recognizes some part of the invading disease-causing particle as a lock (called an *antigen*) and then creates a key (called an *antibody*) to block it. The key closes the lock (they fit together) and nothing else can happen.

<u>When the industry produces a vaccine</u>, it imitates the natural process: i. a stable part of the virus is chosen to avoid that mutations make the vaccine ineffective too quickly, ii. a product is made that once injected will trigger the immune system and its memory. iii. to control a pandemic, at least half the population has to be vaccinated. Some vaccines are more successful than others, as the viruses that do not mutate are easier to fight. Virus that mutate can escape their vaccine quite easily (we call this Darwinian selection), the flu and the SARS-CoV2 are in this category.
One can include different antigens in the vaccine to make it polyclonal (poly = multiple, clonal = copy), to increase the chances of not losing efficacy.

But this takes time, lots of time. The cycle of the industrial production of vaccines is quite slow; one needs to find the good target (the good antigen/lock), then develop the good key, then test for safety and efficacy. And if the virus escapes, we will have to re-do it all over again.

[Note: A possible faster way to develop vaccines is based on RNA technology – but it is not yet widespread].

<u>The natural immunization is the same</u>, but happens inside our bodies, is "always on" at all times, and repeats itself naturally whenever needed. It takes ONLY a few weeks to become immunized.

But in dealing with pandemic, the natural immunization has an enormous advantage. Because of the diversity of individuals, both the recognized part of the viral particle as well as the key that will be generated will be different among a population. Natural immunization will generate millions/billions of different keys by having each of us generating a different key. It is hence a system based on *polyclonal* (poly=multiple; clonal=copy) antibodies.

Having millions (or billions) of solutions/keys to lock and block the virus, makes it very hard for any virus to be effective, and makes the infection of additional persons very difficult thus protect the whole population. If the virus evolves, NO Problem, many people will spontaneously develop in their bodies some immunity, protecting the group.

<u>Passive immunity</u>, on the other hand, is injecting *ready-made* antibodies, produced in laboratories. This is a single ready-made key able to fit a specific lock. This is the principle of monoclonal (mono = single; clone = copy) antibody therapy (aka. serotherapy). This explains why the serum of the infected people who already healed can be used to treat and protect the newly infected people. However this does not work for all the viruses – for SARS we still do not know.

There are a few reasons why efficient and durable vaccines are hard to obtain for respiratory viral infections:

- There are several different viruses that can cause a common cold (*Simancas-Racines et al., 2013*). Getting vaccinated against a specific one will protect against that virus only. Since there are a myriad of viruses that are responsable for the common cold, being protected against specific virus will not prevent getting a cold.
- Sometimes, more than one virus is active at the same time, so that a patient gets infected by 2 different viruses in the lungs. This has been shown to be the case with Covid19.
- All living organisms mutate (= change). Viruses can evolve particularly fast. Furthermore, some viruses tend to mutate recognizable parts of themselves faster than others, just to escape the natural immunity or the vaccine immunity. This is particularly the case for the viruses that cause the common cold and the seasonal flu (*Keilman, 2019; Webster and Govorkova 2014; Simancas-Racines et al., 2013*).
- For SARS-CoV2, the reported mutation rates are likely to generate **30 different variants** per year [see Note 2].

Therefore, therapies based on monoclonal antibodies (whether monoclonal antibody therapy or vaccines based on specific parts of viruses) become *obsolete* as viruses mutate and become resistant (*Berry, 2018*). In the case of the seasonal flu, vaccines have to be updated regularly in order to counter new viral strains, a time-consuming and costly process whose efficiency ranges between 10-60% and that easily leads to stockpiles of unused batches (*Erbelding et al., 2018; Soema et al., 2015*).

As viruses mutate, all "older" versions of viruses will still be killed by our immune system, but newer versions will be able to circumvent our protection and consequently a natural polyclonal-based strategy presents advantages.

A natural polyclonal protection is *herd immunity* (or *protection*), where a group of individuals exposed to a virus, in which each individual will construct a different personal key to block an individually recognized lock that will then prevent viral transmission and slow an epidemic on a population scale. This mass immunization can also be achieved by mass vaccination, but in the latter case, herd protection depends on the type of vaccine (in which case the vaccine has to achieve solid immunization). Herd immunity has an important role in preventing epidemics and disease elimination or eradication (*Rachid et al., 2012; Smith 2019*). When a vaccine is not that effective, herd immunity becomes a social need.

We all immunize ourselves hundred of times a day against many things, without any side effects, our industry cannot do the same as fast. Even if it will have to play an essential role against many diseases.

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