Beyond just counting…Part 3 – human guinea pigs for saving the world? - Don't throw established scientific and medical methods over board!

In view of high numbers of death because of COVID-19 and the necessity to release the world wide 'lockdown', the idea to divert from established rules for testing drugs to help patients and to come up with a vaccine as soon as possible is floated around.

For those who are unlucky to catch the germ and develop the full-blown disease, the SARS-CoV-2 virus causes a life-threatening condition. But, in its historical context, the COVID-19 pandemic is one of a more or less regular occurring pestilence castigating mankind (1). A very normal reaction to such a thread is trying not to be infected. In times of cholera and plague, preventive measures included not to let ships enter the harbors, giving not much attention to what happens to those on board. One wonders whether the present pandemic brought back such reactions. To quarantine people arriving by plane from a foreign country seems to be acceptable, but not to allow cruise ships with diseased passengers on board to enter the harbor and release the passengers on land is a reminder on reactions which were thought to belong to the medieval world.

Likewise, not much though was given to ethical norms in former times, while testing methods suitable to avoid getting the disease. One of the highlights in preventive medicine is the first vaccine trial against smallpox. The disease 'killed kings and peasants alike' and about 20% of the population's vision was severely affected by the virus or even leading to blindness (2). It was known at that time, that cowpox caused mild pustular to milkmaids being in contact with infected cows but they seem not to catch variola. Edward Jenner became well known in history by inoculating an eight-year-old-boy with cowpox. Then he waited for 48 days and inoculated the boy with material taken from someone with active smallpox. The boy remained free of variola and the result of the trial was made known in 1798 (Case 17). It seems that a similar trial never would pass an ethic committee today. Yet, at the end of March this year, a publication within the Journal of Infectious Diseases, suggested infecting volunteers with the virus to shorten the development of a vaccine against SARS-CoV-2 (3). As a response, Science, one of the leading scientific journals, thought it advisable to warn not to lower scientific standards even in a crisis like the COVID-19 pandemic (4).

Therapies in an emergency

Historians, see epidemics, as caused by COVID-19, as a challenge to society disclosing structures within the society formerly not that open to see. As a result epidemics might 'reveal what really matters to a population and whom they truly value' (5). The unprecedented number of severely diseased patients suffering from a so-far unknown virus overwhelmed the curative system of a number of countries and created a crisis situation, which seemed to have allowed to divert from quality standards in the use of different treatment regimens and drugs being used. Commonly drugs approved for other diseases were applied, such as the antiviral *remdesivir* and *chloroquine*. For instance, when it comes to test drugs promising in animal studies to work against SARS and MERS the established method before their bedside use should be randomized

clinical trials (RCT). However, it was argued that because of the 'urgency of the situation' essential steps and conditions of RCT might be 'dispensable', (here: for the use of hydroxychloroquine). This view was opposed in pointing towards a number of misjudgments in the interpretation of the treatment results and the suitability of the drug being used worldwide (6).

Developing and test vaccines under time constrain

There is no doubt, that medical doctors urgently need reliable treatment regimens for their patients. SOLIDARITY is an attempt, launched by WHO to collect reliable results of treatment attempts worldwide (7). Beyond, the need to treat patients suffering from the Covid-19 virus, of even more public health interest is the development of a vaccine, not only to prevent millions of people to get infected but, equally important, not to be harmed from the inoculation. A rigorous scheme in vaccine development and testing has to be observed. It takes a long time from the development of the serum through laboratories and animal studies towards clinical trials. In principal, the latter consists of three to four phases. In phase I the trial vaccine is given to a small group of healthy people to test the overall reaction against the preparation. The next group tested are those, who have the characteristics of those who should be protected by the vaccine. The third phase is the most time consuming in that the safety and efficiency of the vaccine is tested with thousands of people. This, in an ideal situation, has to be done in the environment of an ongoing epidemic. People who get the trial vaccine are living within the environment of the ongoing epidemic. The vaccinated people are as exposed to the virus as the ordinary population. In order to speed up the process it has been suggested to use volunteers, who get the vaccine and being inoculated with the virus. This step in a trial actually is being reserved to animal studies. A human challenge study has been suggested (3), and an ethical frame work for a controlled human infection has been published (8).

Despite the risk for volunteers, even the application of well tested and licensed vaccines can be problematic. Currently no vaccine against COVID-19 is available, activist opposing vaccination already starting to campaign against it. Presently the 'Microsoft Bill Gates' and his foundation are in the focus of those groups. He is accused of a number of serious mishaps related to vaccination campaigns especially in third world countries. The Foundation, for instance, supported a polio eradication program in India, which was supposed to be linked to the occurrence of 'non-polio acute flaccid paralysis (NPAFP) epidemic'. There are numerous additional accusations blaming the Foundation and the WHO for mishandling vaccination programs. To avoid to endanger the acceptance of vaccines, once they are available, the most stringent procedures in the development and the testing of the vaccines should be observed.

Still, the routine handling of a newly introduced vaccine could turn out quite problematic, even it was developed by observing all the rules. A recent example (not COVID-19 related), is the vaccine *Shingrix*, aimed against the very painful shingles disease. (The vaccine has nothing to do with WHO or Bill Gates.) The side effects seem to be difficult to tolerate and can prevail for several days. Very unlucky ones might experience an anaphylactic shock. To describe this as a 'serious allergic reaction' is an understatement, since it is a life-threatening condition.

Genetically engineered proteins

Ways and means of vaccine development strategies used to protect from various infectious diseases, don't differ much in principle and basically aim to stimulate the human immune system, in one or the other way to counteract the replication of the virus. The immune system however is a very delicate one. How delicate the system reacts was discovered while working for a vaccine against the orthopneumovirus also called respiratory syncytial virus (RSV). (A virus with usually cause mild respiratory infections for young children but occasionally the disease can turn out to be serious in case of premature babies and elderly adults). In testing a trial vaccine to prevent RSV, two children dyed. The vaccines protection properties was based on genetically engineered proteins to trigger an immune response against the virus spike protein, which is being instrumental in the attachment of the virus on the human cell. The vaccine triggered antibodies bound to the surface proteins of the virus but did not prevent the virus from infecting the cell giving cause to 'haywire immune response' (9). Finally, it was found out that the reaction was different when comparing the effect before- in comparison after the virus attached to the cell. Only the configuration before fusing with the cell worked (10).

mRNA vaccines

The example of a vaccine based on a genetically engineered protein, is a very delicate, and innovative way to work against a structure of the virus and immobilize it. Similarly, advanced are efforts to develop so-called mRNA vaccines. Experts claim this technique 'revolutionize' vaccine developments. Actually, without mentioning, let alone explaining what might be behind mRNA vaccines, and to cheer up the general public worldwide, a picture of a Ms. Jennifer Haller seemed to have been broadcasting throughout the world, made available by Moderna, a biotech enterprise involved in the race to come up with a vaccine as soon as possible. The idea was to let us know, research and development for vaccines are going on at the same time as being under pressure during the 'lockdown'. In fact, the optimistically smiling Ms. Haller was the first one to be injected with a newly developed mRNA vaccine. This was being done to test whether she and other volunteers participating in this step of vaccine development will tolerate the vaccine as such and develop some immunity against the coronavirus. Up to now no mRNA vaccine made it to a phase III clinical test. It is claimed that the technology of such vaccines will be very safe, being manufactured more easily and could be adapted to be protective for a wide spectrum of infectious diseases and in cancer (11). In principle the technique works while introducing an mRNA sequence with the code for a specific antigen into the cell to stimulate the immune system to block the particular step within the replication of a given virus. The unstable mRNA has to be brought into the cytoplasm 'hooked' on some sort of 'transport virus' (vector) claimed not to be harmful to the host. However, one of the problems to come over in the development of such vaccines is the possibility of an immune response of the host against the vector. So, for instance one of the approaches tested presently is to use a 'nonreplicating version of adenovirus-5 (Ad5). The virus as such (when *no*t being used as a vector) is causing the common cold. What must be prevented in this case is an immune response of the host against the vector based on the immunity against AD5 as such, if the host before got an AD5 infection (9).

Inactivated or weakened whole virus

Besides mRNA vaccines and the engineered protein technology, the 'old school' method, in memory of Doctor Jenner, is to stimulate immunity against a virus infecting the host is using an inactivated or weakened whole viruses as a vaccine. A China-based group of developers recently reported to have tested a chemically inactivated version of the SARS-CoV-2 virus with rhesus macaques being infected with COVID-19 in their lungs (12). However, it is criticized, that the number of animals is too small to indicate a significant statistically relevant difference to the controls. Another criticism points out, that the virus challenging the monkeys might be different from the virus that attacks humans (13). But the developers claim to have used antibodies from three kinds of laboratory animals and challenged the monkeys with strains of the virus derived from patients from different countries. The results so far achieved encouraged the company to test the vaccine with 144 volunteers in China.

Conclusion

This tour d' horizon hopefully is convincing to support the stance to rush through vaccine developments disregarding established norms might be contra productive. The public must be convinced that every precaution was observed to minimize possible serious side effects which finally might endanger the acceptance of the vaccine and stimulate serious objections from vaccine opponents. So-called human challenge studies have a long and at times ill-reputed history, let alone the horrifying medical experiences of the German Nazi doctors (14). Up to more recent times such experiments had been done by testing malaria, cholera, dengue fever vaccines and including also vaccines for the flu (14). Nowadays, these trials undergo 'extensive ethical reviews' and even those working in this field warn against such experiments for the new coronavirus. Opinions against such an undertaking are that the course of the COVID-19 disease can take is still not fully understood, so that the risk taken cannot be fully assessed. The high-quality standard the challenging virus of which the volunteers will be exposed cannot be assured yet, and an effective drug against the disease, the virus can cause, is still not available. Let us hope, that the social, economic and political aftereffects of the pandemic in future will not so devasting, that the availability of a vaccine against the virus, already in decline so far, is the least problem on hand.

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The manuscript was written by Frank P. Schelp
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