Covid-19 vaccination – with informed consensus, please!

Two mRNA vaccines were approved in a hurry to cope with the Covid-19 pandemic. Immunization campaigns were launched, but many questions about the safety of the new developments remain.

Vaccines are powerful means of public health (1). Annually, vaccination might avoid around 6 million death worldwide (2). However, effective medications also have side effects. This is equally true for vaccines and drugs. Drugs used in clinical practice should be authorized by proficient institutions set up by the government. Authorization depends on the proof that development and testing were meticulous and followed established procedures. One of those methods testing drugs for effectiveness and against side effects are double-blind controlled trials.

Testing the safety of vaccines

There are appropriate methods for testing vaccines as well. In principle, they contain preclinical testing of human cells in vitro and animal studies in the laboratory. The testing in vivo with volunteers, in general, follows three phases: Testing for safety and immunogenicity in a limited number of individuals in phase 1. For phase 2, this test is repeated in several hundred's and phase 3 in several ten thousand people. In phase 3, participants are involved who live where the germ is spreading among the population. Testing includes two groups, those vaccinated and the other receiving a placebo instead of the vaccine. After phase three, the vaccine should be approved. Through surveillance, safety, and efficacy are assessed in phase 4, while the safety and effectiveness are considered (3).

While medicines are used to treat diseases, vaccines' purpose is to prevent diseases. The majority of those immunized are healthy. The injection is supposed to trigger the immune system of the organism to reject invading germs. But the system isn't flawless. Disasters not only occurred along with the widespread use of particular drugs but also in the application of vaccines.

Misfortunes in the use of drugs and vaccines in the past

As far as drugs are concerned, disasters happened "due to the incomplete and thorough clinical studies of the active pharmaceutical ingredient and the excipients as a whole or due to the inadequate post-marketing surveillance of the specified product" (4). Thalidomide, for instance, was widely used in the 50th to the 60th of the last century to treat morning sickness of pregnant women. The use of the drug for pregnant females had to be stopped since it was found to cause severe birth defects. It is assumed that from 10.000 embryos affected, 40% died, and those survived had serious defects on limps and other organs. The drug still is in use to treat complications in leprosy and cancer. Disasters like this might involve thousands of individuals or patients. It is no consolation for those harmed that the drug might be of value once the indication for treatment changed.

An example of a “fiasco” in “post-marketing surveillance” for a vaccine is linked to the Salk polio vaccine. Here two batches of the formalin-inactivated Salk vaccine were not tested for safety and were contaminated with live poliovirus. Forty thousand individuals suffered from severe side effects, in addition to 51 cases of permanent paralysis and five death (5). An overview of what happened in the past is given by Knipe et al. (2020), pointing out that comprehensive safety testing is based on experience with prior vaccines (3). Numerous unforeseen reactions observed in the past should remind us that the human immune system reacts in a very complex way. An excellent example of complex immune responses in the course the SARS-CoV-2 virus follows within a diseased person. In unfortunate cases, the patient's life is threatened by a ‘cytokine storm,’ and the infection might attack almost every organ of the body.

Additional examples of “unexpected” immune reactions were mentioned in this blog by hinting towards the protective effect parasitic infections have on diabetes mellitus. Astonishing immune responses with the zika- and dengue virus and the need to develop a vaccine towards a strain of poliovirus brought into the population by vaccination against the poliovirus were described. Extreme precaution in the development and application of vaccines is very much justified.

How a vaccine works in principle

To understand the basic function of a vaccine is not that difficult while recalling what Edward Jenner, the father of vaccination, achieved. Edward Jenner was successful in the outgoing 18th century. He triggered a protective immune response in his gardener's young son by first inoculating cowpox, harmless for humans, waiting for 48 days, and then inoculated active smallpox material. Finally, he could report that this exercise worked, in that the human guineapig did not develop the human strain of smallpox.

At that time, no ethical committee demanded a lengthy justification for the experiment. Vaccine development and testing have, of course, much improved. Techniques did not change over the last decades. So, for instance, a China-based group tested a chemically inactivated virus of the SARS-CoV-2 virus with rhesus macaques and infected the animals with Covid-19 in their lungs (6).

How mRNA vaccines should work

However, rapid development in molecular medicine and technical innovations now divert from established methods in creating new vaccines. The term ‘mRNA vaccines’ is mentioned often but seldomly explained how they work. Expert opinions are quoted in assuring that the technology is very safe, vaccines are easily manufactured and can protect for a broad spectrum of infectious diseases and even cancer (7). From the viewpoint of science, the technique indeed is a ‘smart’ approach.

To comprehend the basics of the approach, one has to remember some forgotten high school knowledge. Genetic information is stored in DNA and RNA in the letters called nucleotides.

Complimentary base pairs are formed through hydrogen bonds, in that guanine binds with cytosine, adenine with thymine, and uracil instead of thymine as far as RNA is concerned. The information on the genetic code stored in the DNA is translated by RNA into protein pieces called peptides. 'Transport' RNA (tRNA) delivers the respective amino acids and attach the amino acids with the help of ribosomes according to the code of the 'messenger' RNA (mRNA).

In case of the mRNA vaccine, the mRNA is a copy created from a segment of the DNA from the virus genome coding the 'spike protein' by which the virus attaches itself to the cell surface. Not the virus but only the mRNA then triggers the host cell to synthesize proteins. As far as the SARS-Covid-2 virus is concerned, the human cell produces then the virus spike protein. This results in an immune response from the human host against the spike protein, which is supposed to fight against the invasion when the real virus is attacking.

mRNA and genetic engineering?

According to what is being explained by Wikipedia, mRNA vaccines might be labeled as tools for genetic engineering. Until recently, genetic engineering was a hotly debated issue; for instance, food items originated from the genetic engineering of plants.

An outcry against genetic engineering involuntarily sparked a Chinese scientist at the end of 2019. He helped to alter two babies against HIV genetically. Finally, he was sentenced to 3 years in prison 'because he conducted 'illegal medical practices' (8). This extreme example of genetic engineering during pregnancy might be far-fetched and not comparable to mRNA vaccines' potential dangers. But then, disastrous intervention turning out to be unsafe might add a noxious blow to the world's overall grim situation into the first half of the 21st century. One should not hope that this will happen. However, since the outbreak of the so-called pandemic spread of the SARS-CoV-2 virus, it was forewarned not to hurry with drug treatment and vaccines release. Being cautious with the mRNA vaccine is essential since it's based on relatively new technology (3, 9-11).

Two mRNA vaccines against Covid-19 now in the forefront

In fact, up to the end of 2020, mRNA vaccines were not yet approved. Many pharmaceutical companies started a race in developing vaccines against SARS-CoV-2. Some companies were supported substantially by governmental and NGO funds. The stock market reacted in favor of these attempts and was further pushed up by promising press releases. To follow up, who was doing what and what success was achieved became more and more confusing. Two companies using mRNA technology seem now to be at the forefront. These are the USA-based Moderna's vaccine and the vaccine from Pfizer and BioNTech cooperation. Both vaccines are currently approved as emergency measures and started to be used in the USA, Great Britain, and several European countries since the end of 2020. On the 1st of January 2021, the World Health Organization (WHO) approved the Pfizer/BioNTech vaccine for emergency use too. By following the Food and Drug Administration (FDA) of the USA. The FDA approved this vaccine

after a meeting of the Advisory Committee on the 10th of December 2020. On the 18th of December 2020, the Moderna's vaccine was authorized by the FDA as well to be used for individuals of 18 years and older. The procedure was termed as emergency authorization. Moderna claims that 7.000 participants in the trial were over 65 years old, and 5.000 under 65 had diseases putting them under higher risk when being infected. More than 11.000 people were from 'communities of color' (12).

Maybe, two publications helped to pave the way for the approvals. These are the "preliminary report, of a first human phase 1 clinical trial" with a small number of participants vaccinated by Moderna's product (13) and the preliminary report of a phase 1/2, single-blinded, randomized control trial, involving 1077 participants with the Pfizer/BioNTech vaccine, including as well as an 'interim analysis' of four, still ongoing, blinded, randomized controlled trials in Brazil, South Africa and the UK (14). The urgency in the development of vaccines against Covid-19, using an entirely new technique, was cheered as the breakthrough of the year by Science (15) and the Editor in Chief in the last issue of the Journal in 2020, as a "testament to the work of so many dedicated scientists today and in the past."

Cheering the progress and the reactions of opponents

Politicians and the mainstream media far and wide joined in cheering the progress. At the same time, vaccine opponents and skeptical voices started to be suppressed by popular media such as YouTube, Facebook, Twitter, etc. By and large, it seems that skepticism is widespread. It is difficult to imagine that manuscripts published as preliminary reports would have passed rigorous referee judgments before being published in Lancet and the New England Journal of Medicine formerly. The papers are difficult to read, especially for those not familiar with the field of immunology. It is claimed that the Moderna and the BioNTech vaccines have an efficiency of 90 to 95% (12). Critics point out that this cannot mean that 9 out of 10 persons will be saved from the virus. Given the population of Germany, for instance, 83 million, that would mean that there are still 8.3 million infected. This will be five times more than presently recorded by the government's Public Health Institute (RKI). Instead, the figure relates to those in the trials found to be infected. It is argued that the efficacy accounts only for 0.84% (*see the end of the manuscript).

The report to the FDA is based on the trial mentioned before and substituted with additional results obtained from the USA, Argentina, Germany, and Turkey, but omitted data from the UK. The report was also met with reservations, claiming that adverse effects were hidden in the annexes. As submitted to the Advisory Committee Meeting on the 10th of December 2020 from Pfizer/BioNTech, it obtained numerous additional material for consideration. The study itself included 43.651 volunteers vaccinated either with the vaccine "BNT162b2" or a placebo. During the following observation period, 8 of 18.198 vaccinated persons tested positive for the Covid-19 virus, and 162 from 18.325 persons not receiving the BNT162b2 vaccine at least got a positive PCR test.

In the appendices to the report of the Pfizer BNT162b2 trial, 'adverse events' for 21.621 vaccinated participants and 21.631 volunteers receiving placebos are listed. Within the vaccinated group, any adverse event happened to 5770 (26.7%) persons in contrast to 2638 (12.2%) placebo recipients. However, the number of 'related' events to the vaccinated individuals, 'assessed by the investigator as related to the investigational product,' happened to 4484 (20.7%) persons.

Participants with comorbidities are more likely prone to severe side effects than apparently healthy persons. In fact, from 37.706 participants altogether, 7.743 (20.5%) had comorbidities according to a classification of an index, considering AIDS, cancer, cardiovascular diseases, and other chronic diseases (16). It appears that comorbidities within the vaccinated compared to the placebo group are more or less evenly distributed. It cannot be overlooked that 'related adverse events' in the vaccinated groups, with 20.7%, exceeds the placebo group with 5.1% by far.

To receive vaccine shots usually hurts, and side effects must be expected. That is true for the Covid-19 mRNA vaccines discussed here as well. A severe case is described by a volunteer injected with the Moderna's vaccine. The paper reporting about this somehow cynically was subtitled with 'take Tylenol and suck it up' (17). Pain has to be tolerated twice because two injections are required three weeks apart. For Pfizer and Moderna's vaccines, pain in the arm, headache, and muscle pain are recorded. About 2% of the recipients for both vaccines developed severe fever bouts. The companies expect to vaccinate 35 million people worldwide soon. That might allow vaccination opponents to hint towards the substantial figure of 700.000 people coming up with fever of 39^0C to 40^0C.

Questions and problems remaining

Before Moderna's vaccine authorization, Science mentioned that the product is 'absolutely remarkable since no one vaccinated got severe Covid-19. But Science also reminded the reader that questions still have to be answered. It is not established how long the protection will last, how safe the remedy actually is, and how it could be produced for millions of people observing a cold chain of -20^0C (18). Similar questions are still not answered for the Pfizer/BioNTech product as well. Let alone that the latter one requires even a temperature to remain active of -70^0C. The low temperatures are necessary since both vaccines deliver the mRNA into the human cell, wrapped into lipid nanoparticles.

Allergic reactions

The temperature sensitivity of the lipid nanoparticle is not the only problem for both vaccines. The compounds contain polyethylene glycol (PEG). The subject is known to occasionally causing anaphylaxis, a life-threatening, allergic reaction. Some people receiving the vaccines might have antibodies against PEG, and that placing them at risk. Approximately two weeks after starting to use Pfizer/GeoNTech vaccine, eight people developed severe allergy-like

reactions. PEG hasn't been used for vaccine developments yet, and both vaccines, Moderna and Pfizer, didn't include participants known for allergies in their trials (19).

Targeting the spike protein

Once the vaccines are in everyday use worldwide, extraordinary events might happen and undermine the trust in vaccines and the mRNA vaccines in particular. One of the weak points might be that vaccines' target is the spike protein of the virus. Spike proteins are standard tools for viruses to attach to the human cell. An attempt to develop a vaccine against the respiratory syncytial virus (RSV) caused some serious side effects during the trial periods, with even two children died. The immunization resulted in the desired effect of creating antibodies against the virus spike protein but did not prevent the virus from infecting the cell. Instead caused a 'haywire immune response' (20). It was found out that the effect was different when comparing the reaction before- in comparison after the attachment of the virus to the cell (21). But no such effects have yet been reported from the trials discussed here.

Benefits for pharmaceutical companies, compensation in case of side effects, and forced vaccination

If serious misfortunes happen, mistrust might be directed not only towards the products but also against the producer. This applies to vaccine developers' attitudes, cashing on huge gains, even before there is a vaccine finally developed (22). Hinting towards social pressure to enable forced vaccination (18) (you know we could open up our community, except for people like you) is not well taken by the populace.

One wonders, what happened recently in India will become a common scenario once vaccination is imposed worldwide and severe side effects accumulate. A volunteer, who took part in a vaccination trial, sued the Serum Institute of India (SII) with USD 689.000 (50 million rupees) after falling seriously ill. The trial of the SII used a vaccine developed by the University of Oxford and AstraZeneca. The SII called the allegations 'malicious and misconceived' and threatened him with a countersuit of up to 1 billion rupees. The company informed the volunteer that the complications he suffered were independent of the vaccine trial he underwent (23).

Outlook

Many unsolved questions remain, such as whether immunization will indeed prevent infection and whether protection will wane quickly (24). The trials' final results, especially from the third phase, are not yet published as peer-reviewed papers. Efficacy and side effects are just only mentioned in press releases. Certain groups of the populations were not included in the trials. That relates to children and pregnant women.

The stability of the mRNA is not yet known for the two vaccines discussed here. Generally, it is known that the mRNA's stability tends to be weak and disintegrate rapidly among physiological

conditions. The sufficient production of antibody, however, depends on the stability of the mRNA. The purpose of the lipid nanoparticles wrapped around the mRNA is to stabilize the particle. The stability of these particles, as such, is known to be weak and needs very low temperature to be stored. This most probably will create logistic problems when vaccination started to be in full swing.

It is not advisable to stimulate an attitude of rejection against these new techniques. There is the potential to create new vaccines against a wide range of diseases. For this, an 'elegant' scientific approach is used, with low costs for the final product. This all in all should be of great benefit for public health. However, what stimulates deep routed suspicion about the mRNA vaccines' safety is the unusual hurry in testing and suspected forced immunization. We don't know how 'informed' the boy's parents had been while Jenner was testing his theory about the protection of cowpox against smallpox. While the mRNA vaccines are supposed to be used to immunize millions and millions of people, this is a trial of untold magnitude with an incalculable outcome. Research projects involving volunteers, patients, and other defined groups of people have to pass ethic committees before going ahead with the project. One of the major requirements is to assure informed consensus by the participants. This should be an obligation, not only for those volunteering in the trial phases but for the overall population. Everybody should be in a position to make an informed decision to be vaccinated or not.

* Within the vaccinated group of 18.198 individuals, eight persons were infected with the virus, while 162 participants out of 18.325 of the placebo group tested positive. This is 0.044% in the vaccination and 0.885% in the placebo group. The calculation of 1 – (0.044/0.884) equals 0.950, that's 95%. This calculation relates not to 1 out of 10 individuals immunized. It is the relative reduction of risk associated with those infected in the given groups. It doesn't display the reduction achieved within the total population participating in the vaccination campaign. The absolute decrease for the group immunized would be 0.884 – 0.044 = 0.84%.

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