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ИСТОРИЯ С БОЛЕЗНЬЮ МАРЕКА ПОУЧИТЕЛЬНА В ОТНОШЕНИИ ПАНДЕМИИ COVID-19?

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Резюме: Болезнь Марека (БМ) — смертельное вирусное заболевание кур. Вплоть до 1960-го года БМ была сравнительно легким заболеванием с невысоким уровнем смертности. К 1970-му году в птицеводстве стали преобладать мегафермы, и в это время БМ превратилась в реальную угрозу. Для того чтобы справиться с этой угрозой в начале 70-х годов XX века была разработана и внедрена вакцина против БМ. Провакцинированные куры редко заболевали БМ. Однако за прошедшие 50 лет вирус БМ становился все более смертельным, и теперь 100% невакцинированных кур умирают через две недели после инфицирования наиболее вирулентными штаммами, а именно такие и распространяются вакцинированными птицами. Вакцина против БМ является субоптимальной, поскольку уменьшает проявления болезни, но не предотвращает инфицирование и распространение вирусов. Многочисленные исследования позволяют предположить, что, будучи субоптимальной, вакцина против БМ не только допускает, но и стимулирует эволюцию штаммов вируса все большей и большей вирулентности. Вакцины от COVID-19 также относятся к субоптимальным. В связи с этим имеется вероятность того, что использование некоторых таких вакцин может способствовать и стимулировать эволюцию штаммов вируса SARS-CoV-2 возрастающей вирулентности, что может привести к зависимости человека в глобальном масштабе от вакцин против COVID-19, а эти вакцины могут на каком-то этапе подвести из-за развития вакцинорезистентности.

Ключевые слова: болезнь Марека; COVID-19; оптимальные и субоптимальные вакцины; вакцинная резистентность.

REGARDING THE COVID-19 PANDEMIC, IS MAREK'S DISEASE A CAUTIONARY TALE?

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Abstract: Marek's disease (MD) is a deadly viral disease of chickens. Prior to 1960 MD was a relatively mild disease, with a low mortality rate. By 1970 large scale corporate mega-farms were dominating the chicken industry, and MD became more threatening. A vaccine for MD was, therefore, introduced in the early 1970s. Vaccinated chickens rarely become ill with MD. However, over the past 50 years the MD virus has become increasingly deadly, such that 100% of unvaccinated chickens die within 2 weeks when exposed to the most virulent strains, which are shed by the vaccinated chickens. The MD vaccine is a sub-optimal vaccine in that it reduces symptoms but does not prevent infection or

transmission of the virus. Studies have strongly suggested that, because it is a sub-optimal vaccine, the MD vaccine enables and drives evolution of increasingly virulent strains of the virus. The COVID vaccines are also sub-optimal vaccines. This raises concern that the COVID vaccines might enable and drive evolution of increasingly virulent strains of the SARS-CoV-2 virus and cause the global population to become increasingly dependent on COVID vaccines, which may eventually fail, due to evolution of vaccine resistance.

Key words: Marek's disease; COVID-19; optimal and suboptimal vaccines; vaccine resistance.

MAREK'S DISEASE

Marek's disease is a deadly viral disease of chickens [1–19]. It is due to an oncogenic alpha-herpesvirus that, now, rapidly causes malignant, lethal T-cell lymphoma.

Prior to 1960 Marek's disease was a relatively mild viral disease [1]. It primarily caused transient polyneuritis and was not a huge threat on family chicken farms. The mortality rate was quite low. By 1970 large scale corporate mega-farms were dominating the chicken industry, and at about the same time Marek's disease threatened to decimate the global mega-farm chicken industry. A vaccine for Marek's disease was, therefore, introduced in the early 1970s. Now the vast majority of the world's 20 billion chickens are being vaccinated. Vaccinated chickens rarely become ill with Marek's disease.

However, over the past 50 years the Marek disease virus has become increasingly deadly [1–11]. Now, when unvaccinated chickens become infected with the most virulent strains of the Marek virus, they develop malignant tumors, paralysis, severe brain damage, and 100% die within a couple of weeks [1][1]. The primary source of their infection is the shedding of virulent strains by vaccinated chickens. The Marek virus has become one of the deadliest viruses in history, and industrial chicken farms have become totally dependent on vaccination.

OPTIMAL VS SUBOPTIMAL VACCINES

An *optimal* vaccine prevents infection and transmission. By preventing infection, it prevents illness. An optimal vaccine does not just protect the vaccinee from developing severe illness (when that individual is exposed to the virus); it prevents the virus from successfully entering the vaccinee's cells and replicating within them (i.e., prevents infection), and it, thereby, prevents that individual from shedding and transmitting the virus. An optimal vaccine does not just reduce symptoms; it prevents both infection and transmission.

THE MAREK'S VACCINE IS A SUBOPTIMAL ("LEAKY") VACCINE

Unfortunately, the vaccine for Marek's disease provides only *suboptimal* immunity against the Marek virus [1, 4, 8, 9]. When a vaccinated chicken subsequently becomes infected with the Marek virus, the vaccine partially blocks entry of the virus into host cells, thereby reducing the severity of symptoms from Marek's disease, but does not completely stop the virus from entering cells and replicating. The vaccine does not eradicate the live virus within that chicken, nor does it prevent transmission. Although the vaccine protects the chicken from severe illness (i.e., reduces symptoms), the live virus continues to live within that chicken, replicates within that chicken, and is shed by that chicken [1, 4, 8, 9][2, 3]. In fact, when vaccinated chickens become infected by the Marek virus, they cumulatively shed 10,000 times more virus than do infected unvaccinated chickens (who quickly die and, thereby, stop shedding) [1].

[1] "There is a theoretical expectation that some types of vaccines could prompt the evolution of more virulent ("hotter") pathogens. This idea follows from the notion that natural selection removes pathogen strains that are so "hot" that they kill their hosts and, therefore, themselves. Vaccines that let the hosts survive but do not prevent the spread of the pathogen relax this selection, allowing the evolution of hotter pathogens to occur. This type of vaccine is often called a leaky vaccine. When vaccines prevent transmission, as is the case for nearly all vaccines used in humans, this type of evolution towards increased virulence is blocked. But when vaccines leak, allowing at least some pathogen transmission, they could create the ecological conditions that would allow hot strains to emerge and persist.

This theory proved highly controversial when it was first proposed over a decade ago, but here we report experiments with Marek's disease virus in poultry that show that modern commercial leaky vaccines can have precisely this effect: they allow the onward transmission of strains otherwise too lethal to persist. Thus, the use of leaky vaccines can facilitate the evolution of pathogen strains that put unvaccinated hosts at greater risk of severe disease. The future challenge is to identify whether there are other types of vaccines used in animals and humans that might also generate these evolutionary risks.

Here we show experimentally that immunization of chickens against Marek's disease virus enhances the fitness of more virulent strains, making it possible for hyperpathogenic strains to transmit. Immunity elicited by direct vaccination or by maternal vaccination prolongs host survival but does not prevent infection, viral replication or transmission, thus extending the infectious periods of strains otherwise too lethal to persist. Our data show that anti-disease vaccines that do not prevent transmission can create conditions that promote the emergence of pathogen strains that cause more severe disease in unvaccinated hosts."

[2] "Since the early 1970s, the poultry industry has relied on the use of vaccines to control losses due to MD (Marek's disease). These vaccines, although effective at preventing mortality and tumor formation, do not prevent infection by field. The lack of more effective vaccines has led the poultry industry to rely on the use of multiple vaccine doses and/or multivalent vaccines, significantly increasing vaccination cost. Although several MDV-derived vaccine candidates have been generated, only few have been successful. MDV CVI988/Rispens is the most efficacious vaccine in the market and is considered the gold-standard."

[3] "Marek's Disease (MD) vaccines are described as "leaky," because they protect vaccinated hosts from developing clinical signs of disease, but they nonetheless allow for infection and onward transmission of the virus. This means that the virus can persist and potentially evolve in vaccinated flocks. Two generations of MD vaccines have been undermined by virus evolution, and this evolutionary trajectory has been well documented. Whether the efficacy of existing vaccine control strategies will decline in the future is an open question."

As long as the huge majority of chickens are vaccinated, only a small minority of chickens die of Marek's disease — specifically, the unvaccinated minority. In fact, in recent years unvaccinated chickens who are exposed to the most virulent strains of the virus typically die within 10 days [1]. They develop tumors, become paralyzed, and their brains are destroyed. The primary source of their infection is vaccinated chickens who are doing well themselves but are cumulatively spreading large quantities of lethal strains of the virus. In other words, the greatest threat to the unvaccinated chickens are the vaccinated chickens. As long as the unvaccinated chickens fraternize with only unvaccinated chickens and live in healthy "free range" conditions (i.e., away from mega-farms), they will likely be okay. But, if they are sent to a Tyson chicken farm, which will be full of vaccinated chickens, they will quickly die.

HOW MIGHT MASS VACCINATION WITH SUB-OPTIMAL VACCINES, UNDER SOME CIRCUMSTANCES, GENERATE INCREASINGLY LETHAL VIRAL STRAINS?

There are several mechanisms by which sub-optimal vaccines might, unfortunately, enable and promote the generation of more virulent and more transmissible strains of a virus [1–11]. Two such mechanisms are briefly described below:

Mechanism One — "immune escape": During the process of replicating within vaccinated chickens, the virus, under great pressure to survive, develops mutations, some of which, through natural selection, increase the virus's ability to more successfully evade the vaccine-induced antibodies — thereby, making those strains more virulent, more transmissible, or both.

Mechanism Two — "vaccine-driven evolution of increased virulence": During the process of replicating within vaccinated chickens, the virus, under great pressure to survive, develops mutations, some of which, through natural selection, increase the virus's virulence (or "fitness") and transmissibility — not because the new strains are able to evade the vaccine-induced antibodies, but because the virus otherwise evolves into a more lethal and more easily transmissible virus [1, 3, 6, 8–11]. The sub-optimal vaccine adequately protects the vaccinated chicken from these more lethal and transmissible strains but allows these more worrisome strains to co-exist in the vaccinated chicken and be shed by those chickens. Without these enabling vaccinated hosts, these more lethal strains would kill the chickens they infect and die themselves in the process. The sub-optimal vaccine enables lethal strains to survive and circulate in the community.

The vaccine makes it more likely that more virulent and transmissible strains will appear, persist, and spread [1, 3, 6, 8–11][4, 5].

One or both of the above mechanisms (and/or additional mechanisms) could explain why over the past 50 years Marek's disease has gradually become increasingly severe [1–11]. Prior to introduction of the vaccine, the mortality rate of chickens infected with the Marek virus was quite low. However, since introduction of vaccination, unvaccinated chickens have become more severely ill, have died more quickly, and now have a mortality rate of 100% when exposed to the more virulent strains [1]. The virus has clearly become increasingly lethal over time [1–11]. The more worrisome strains are now referred to as not just "virulent (v)," but "very virulent (v)," and "very virulent + (vv+)" [3, 5, 7][6, 7, 8].

It is as if veterinary virologists have run out of adjectives to denote the extent of virulence.

This increased virulence has made it even more essential to vaccinate virtually all 20 billion chickens in order to preserve the mega-farm model. As long as a huge majority of chickens are vaccinated (with periodically updated vaccines), Marek's disease is kept at bay — at least at the financial level.

POTENTIAL VACCINE RESISTANCE?

However, there is concern (among chicken farmers and veterinary vaccinologists, and perhaps among some smart chickens) that at some point one of the mutations induced by vaccination will become so lethal (vvv+++) that even the vaccinated

[4] "The intensification of the poultry industry over the last 60 years facilitated the evolution of increased virulence and vaccine breaks in Marek's disease virus (MDV-1).

Marek Disease vaccines prevent host animals from developing disease symptoms, but do not prevent them from becoming infected, nor do they block transmission of the virus. Perhaps because of that, those vaccines may have created conditions favoring the evolutionary emergence of the hyperpathogenic strains that dominate the poultry industry today".

[5] "In some cases, vaccination may lead to sudden dramatic increases in virulence. We show that when higher virulence is selected for by vaccines, this may result in increased transmission rates and prevent eradication".

[6] "Recent increases in Marek's Disease (MD)-related mortality and condemnations among vaccinated poultry have occurred in the United States. These increases in disease have occurred approximately 6 years after the introduction of new vaccines. In the late 1970s, following the introduction of HVT vaccines, and since 1992, after the introduction of bivalent MDV2-HVT based vaccines, new MDV1 strains of greater virulence (very virulent [vv] and very virulent plus [vv1] MDV1) were isolated. These viruses are characterized by higher cytolytic activity, unusual tissue tropism, increased atrophy of lymphoid organs, immunosuppression, enhanced capacity to transform T cells, and earlier host death. It has been suggested that emergence of vv and vv1 MDV1 strains may be due to strong selective pressure generated by extensive vaccination and enhanced genetic resistance of commercial flocks".

[7] "Since the introduction of vaccines in the early 1970s, MDV has increased in virulence, and currently, three pathotypes are recognized: virulent, very virulent (vv) and vv+".

[8] "Based on our own research, in recent years an increase in the pathogenicity of isolated MDV strains has been observed (unpublished data). For many years, an increase in the pathogenicity of MDV strains has been observed despite immunoprophylaxis being used in day-old chicks. Such an increase was observed as early as 1997 in the vaccinated flocks of birds. Based on our study and research carried out in other countries, it can be concluded that MDV infection is still a problem for global poultry production. It is of particular concern that the serotype and pathotype apparently highly prevalent in Poland is very virulent".

chickens will die [6, 8, 10][9, 10]. That is, an eventual strain of the virus may become vaccine resistant. If this worst-case scenario were to happen, virtually all 20 billion chickens would be at very high risk of dying. In other words, the chicken industry has become totally dependent on a suboptimal vaccine, and it is conceivable that that vaccine may eventually fail to protect even the vaccinated.

WHY HAS THIS WORST-CASE SCENARIO NOT YET OCCURRED?

It is encouraging that this worst-case scenario has not yet occurred, after 50 years of vaccinating. Perhaps it never will occur. It is important, though, to ask why this worrisome scenario has not yet happened, and to ask how worried we should, or need not, be about the possibility of it occurring.

Possibly, the vaccination campaign against Marek's disease has been "successful" primarily because of an extraordinarily high rate of vaccination. Apparently, the combination of nearly 100% vaccination (on most mega-farms) and a sufficiently effective vaccine (though suboptimal) has kept the infection at bay, at least for the vaccinated chickens. Perhaps the chicken vaccinologists have always been able to develop new vaccines that have adequately countered each new more dangerous variant that has come along. Perhaps this situation has been sustainable, in part, because broiler chickens are sacrificed and sent to market by age 35 days. But how precarious and sustainable is this "success?" Have we just been lucky, so far? What if the vaccination rate falls below a certain critical threshold and/or a new strain develops that is finally able to either fully escape the vaccine-induced neutralizing antibodies, or otherwise becomes so lethal that it kills even the vaccinated chickens? The result would be catastrophic for the industrial chicken industry.

It is possible that the Marek vaccine (including revisions of it) will continue to work adequately well for another 50 years, or more. It is possible that "vaccine resistance" (due to either mechanism one or two, or both) is just a conceivability that will never actually occur (at least to any significant or practical extent) or is so unlikely that we need not worry much about it. But the possibility that a lethal vaccine-resistant strain could evolve needs to be kept at least remotely in mind [6, 8, 10, 13–19].

COULD THE CHICKEN VIRUS "HOP" TO HUMANS?

Another conceivability is that a new lethal strain of the Marek virus (that mass vaccination has enabled) could "hop" from chickens to humans — resulting in a human pandemic of a very lethal strain of the Marek virus. Again, this is probably very unlikely. But such conceivabilities need to be kept in mind when we are messing with immune systems.

WAS IT POSSIBLE TO HAVE PREVENTED THIS HIGHLY LETHAL MAREK'S DISEASE SITUATION?

Could this Marek's disease situation have been prevented? Probably. Marek's disease probably would not have become such a huge problem if massive corporate chicken farms (like Tyson's industrial chicken mega farms) had never come into being. These farms, which house huge numbers of chickens in close, unhealthy quarters, have been perfect breeding grounds for viruses. [9] Within these mega-coops the viruses are free to replicate, mutate, and spread very easily, particularly in already stressed chickens, especially when the vast majority of chickens are vaccinated with a suboptimal vaccine.

If chickens were still raised only in small numbers on small farms, where they are free to roam and would receive excellent care, their own natural immune systems probably would have adequately protected them from the Marek's virus, without need for vaccination. The chicken's natural immune system and the Marek's virus probably would reach a mutually beneficial arrangement whereby the virus could live without causing severe illness for the chickens.

So, a precarious situation that now requires vaccination of 20 billion chickens and kills virtually all exposed unvaccinated chickens probably could have been prevented if we had not allowed the development of corporate Tyson-like mega chicken farms.

WHAT CAN WE DO NOW? RETURN TO THE SMALL FAMILY FARM?

What should we do now, regarding this Marek disease? One option is to "continue *business* as usual." A healthier option, however, is to view chicken farming not as a business, but as a public service. One hundred years ago most farming occurred on small family farms, which were conducted with emphasis on hard work, kind treatment of animals and the environment, and a responsibility to meet the food needs of the community. Excessive profiteering was not part of the culture. Dangerous practices were

[9] "Vaccine efficacy has decreased concomitantly with the increase in virulence of Marek's disease virus (MDV). The constant evolution of MDV has forced the development of new vaccines or vaccine strategies that control the more virulent emergent strains. However, this race between the introduction of new vaccines and the evolution of MDV represents a major threat for the poultry industry. In addition to vaccination, other factors might have contributed to the evolution of MDV (intensive methods of chicken production, early exposure of the chickens to MDV and administration of vaccines at very low doses). From all the possible factors influencing MDV evolution, the effect of vaccination has received the greatest attention. MD vaccines protect with great efficacy against the development of the disease, but they do not prevent infection or transmission. Sterilizing immunity could be a solution to stop the evolution of the virus, but it has been proven to be extremely difficult, if at all possible, to obtain with MDV or with other herpesviruses. Other solutions to improve vaccine-induced protection are discussed in this paper".

[10] "A feature of increased virulence of Marek's Disease Virus (MDV) in the USA has been the failure of successive vaccines and recent outbreaks in both unvaccinated and vaccinated birds caused by more virulent strains of MDV, [which] have prompted fears that the current vaccines may be rendered ineffective with the emergence and spread of more virulent strains".

discouraged. Running a small farm was a meaningful, healthy, challenging, honorable, and interesting existence. Farming was an altruistic endeavor, and the farm was a good place to raise a family.

Unfortunately, corporate mega-farms came into being and made it financially difficult for small farmers to compete. By the 1970s small farming had suffered greatly. It is likely that the Marek pandemic is a consequence of widespread Tyson-like mega chicken farms. The mega farms weakened the chickens, weakened their natural immune systems, and set them up for severe and rapidly spreading infection. This forced need for mass vaccination, which then enabled emergence of increasingly virulent and transmissible strains of the Marek virus, which has now made the chickens totally dependent on vaccines.

It is not too late to outlaw corporate mega-chicken farming and return to the small farm model. There is plenty of land available for the establishment of many small chicken farms. There are many unemployed and sub-employed people (manpower) available. Rather than train underemployed and mis-employed people for relatively meaningless low wage tech jobs, and rather than subsidize people with a "basic universal income," why not subsidize and train people to become successful small public farmers? Part of that subsidization could include rent-free land and funds to create the farm. A new Department of Agriculture, led by exemplary, experienced, altruistic farmers, could oversee this national "small public farms" project and make sure that it works optimally. Agricultural education would be an important component of the project and would be free.

Transition towards the above model and away from the corporate mega-farm model would allow for a transition away from vaccine dependency and may avert a Marek's disease catastrophe. Such a transition would give chickens a chance to strengthen their natural immune systems and become more resistant to severe Marek's disease. Chickens and humans would be far better off.

WHAT IS THE RELEVANCE OF MAREK'S DISEASE TO THE COVID PANDEMIC? IN WHAT WAY MIGHT IT BE A CAUTIONARY TALE?

One could certainly argue that Marek's disease is not relevant to the COVID-19 pandemic. After all, it is a totally different virus, with a totally different mechanism of virulence and transmission, and it is a disease of chickens, not humans. Furthermore, despite the fact that mass vaccination against Marek's disease was introduced over 50 years ago, neither "immune escape" nor "vaccine-driven evolution of increased virulence" has resulted in "vaccine resistance" to a degree that has been disastrous for chicken mega-farms. Moreover, there is controversy and disagreement among veterinary vaccinologists as to how much we need to worry about vaccine-induced generation of increasingly virulent strains of the virus.

On the other hand, it seems prudent, out of an abundance of caution, to at least consider the Marek situation as a possible cautionary tale — at the very least as an exercise in careful critical thinking, as we deliberate the pros and cons of rapid massive COVID vaccination in the midst of a pandemic.

THE COVID VACCINES ARE SUB-OPTIMAL VACCINES

The COVID vaccines, like the Marek's vaccine, are suboptimal vaccines. According to what is known to date: when a person who has been vaccinated with one of the current COVID vaccines is subsequently exposed to the SARS-CoV-2 virus, the vaccine-induced neutralizing antibodies partially neutralize the virus, but do not totally prevent infection. At least some virus is still able to enter and replicate within the vaccinated person's cells, and shedding of virus (by the vaccinated person) still occurs, at least to some degree. Because of the partial protection conferred by the neutralizing antibodies, the vaccinated person becomes less ill from their COVID infection. But, so far, there is no convincing evidence that the vaccines prevent infection of the vaccinated person, or transmission once such a person becomes infected. Again, the vaccines appear to reduce symptoms of infection (which is important), but do not appear to prevent infection or transmission. They are sub-optimal vaccines.

It is possible that future study will prove that the current COVID vaccines, though suboptimal, sufficiently lower the level of infection and transmission so that they diminish, rather than enable and promote, development of increasingly worrisome strains. But this has not yet been established and may not be the case. Until more is known, it seems prudent to keep an open mind and carefully study a broad spectrum of concerns.

Is the combination of lockdown and rapid mass vaccination, in the midst of a pandemic, generating ever more worrisome strains of SARS-CoV-2? Or is lack of sufficient lockdown and lack of sufficient vaccination causing more virulent stains of SARS-CoV-2 to appear?

According to the USA COVID Task Force, led by Dr. Fauci, the main reason for the development of new, more worrisome strains of SARS-CoV-2 is a lack of sufficient lockdown and a lack of sufficient numbers of people being vaccinated. Dr. Fauci states that these two shortcomings have "allowed" the virus to persist, spread, mutate, and, in the process, become more virulent and more transmissible. According to his understanding, the keys to preventing development of more worrisome strains is to vaccinate as many people as possible as rapidly as possible and continue lockdown until an adequate percentage (ideally at least 85%) of the population has become vaccinated.

Dr. Fauci's message is the exact opposite of the Marek disease message. The Marek disease message is that mass vaccination with a sub-optimal vaccine might be causing (not preventing) more worrisome strains to appear and persist. It is critically important to determine which of these contradictory messages is scientifically accurate.

To review, the Marek disease message (the message that contradicts Fauci's message), is that there is at least a theoretical possibility that (via mechanism one) the combination of extensive lockdown and rapid mass COVID vaccination, during an active

pandemic, puts such extreme existential pressure on the virus that it drives the development and natural selection of mutant strains that are able to evade vaccine-induced immunity — thereby, giving the virus the survival advantage it desperately needs. Alternatively, or in addition, the COVID vaccines (via mechanism two) may be enabling (within vaccinated people) the generation and dissemination of increasingly lethal and transmissible strains. In other words, the COVID vaccines may be promoting appearance of more lethal and/or more transmissible strains of the virus, via one or both of the mechanisms mentioned (or via other conceivable mechanisms).

Via the first mechanism, one or more of these new strains may be able to largely or completely evade the neutralizing antibodies — i.e., become resistant to the original vaccine. In such a case, the original vaccine would no longer be protective. The temptation then would be to administer an updated vaccine, one that is able to neutralize the new more worrisome strain. But, then new more worrisome strains might develop, and an ever escalating and increasingly dangerous vicious cycle may ensue, if the plan is to continue to give new updated vaccines for new strains.

Alternatively, or additionally, the COVID vaccines, via the second mechanism, may be enabling (within vaccinated people) and favoring the generation and dissemination of increasingly lethal and transmissible strains that may soon be threatening unvaccinated people and may eventually become so lethal that they threaten even the vaccinated.

I hasten to again add that, for COVID, the above concept of vaccine-driven evolution of increasingly lethal strains is based on theoretical concerns (i.e., represents hypothesis), rather than proven fact. It is possible that these COVID vaccines do not, in fact, drive the development of new significantly more worrisome strains, at least not ones that ever become an unmanageable threat to people who are regularly vaccinated. However, if this hypothesis is true, then unvaccinated people could become increasingly vulnerable to increasingly worrisome strains, unless they eventually become vaccinated. And even the vaccinated may eventually fall victim to vaccine-resistant strains. In that sense, the Human Race becomes increasingly dependent on vaccines, much like the chickens have.

At the very least, it would seem wise to create a Commission (comprised primarily of virologists, immunologists, vaccinologists, and infectious disease specialists — from veterinary schools and schools of medicine — but also including representatives of the public and other relevant disciplines) to evaluate the extent to which the following hypothesis is of concern:

Hypothesis: Rapid mass immunization, with a sub-optimal vaccine, in the midst of an active pandemic, creates increasingly more worrisome and transmissible SARS-CoV-2 strains (via mechanism one, two, both, and/or other mechanisms) that threaten the unvaccinated in the short term and threaten even the vaccinated in the longer term.

The Commission would deliberate this hypothesis transparently, in full view of the public (i.e., on TV and via excellent objective honest journalism) and with participation and input from the public. Dr. Fauci's contradictory hypothesis would be subjected to equal scientific scrutiny.

WHAT CAN/SHOULD WE DO?

If it is concluded that the above hypothesis is most likely correct, what can we do about it? One option would be to transition from a primary trust in vaccines to a primary trust in the ability of the natural human immune system to protect us, assuming we take proper care of our immune system, ourselves, and the environment. With this option the rapid massive vaccination campaign would be stopped, and the lockdown strategy would be gradually (but steadily) disassembled — i.e., pressure on the virus would be markedly reduced. The most vulnerable people would still need to be protected — by preventing exposure to carriers of the virus, particularly carriers of new more worrisome strains (which, ironically, could turn out to be the vaccinated population); but the healthy and less vulnerable could increasingly interact, eventually following only simple commonsense precautions. Schools and universities would steadily re-open, as would businesses, including restaurants. Collectively, people's natural immune systems would gradually strengthen, and herd (natural) immunity would increasingly develop.

Part of this plan would include a commitment (including funding and training) to provide optimal treatment to those who do become severely ill with COVID. (See companion article on Treatment of Severe COVID Illness.) Another part of the plan would be to use the COVID PCR test properly, by paying close attention to the Ct values at which tests are positive. Proper use of the PCR test, including adjustment of the test to detect and quantitate worrisome new variants (if possible), will benefit the care of individual patients and markedly improve the quality of all epidemiologic data [12][11]. (See companion article on PCR Ct values.) Another component of this option is an emphasis on thorough public education, including an emphasis on careful critical thinking and

[11] "Here, we advocate for moderate additional effort during clinical trials to collect and publish data that can inform the risk of resistance evolution.

Much like antimicrobial drug resistance, vaccine resistance can and does evolve. When it does evolve, vaccine resistance is achieved through mechanisms such as serotype replacement, antigenic change, or increases in disease severity.

It is important that the probability of resistance evolution be small because vaccine resistance can negatively impact public health. Should vaccine resistance emerge in the weeks, months, or years between vaccination and exposure, a vaccinated individual could be left unprotected. Should resistance become widespread and common, entire vaccination campaigns could retroactively be rendered ineffective. Moreover, since pre-existing antibodies frequently interfere with vaccine efficacy, we cannot assume that a new vaccine would be capable of restoring protection. Additionally, a large fraction of COVID-19 candidate vaccines target the spike protein of the virus or the receptor binding domain of the spike protein, and so the evolution of vaccine resistance against one vaccine could simultaneously undermine others, an outcome referred to as 'collateral' or 'cross' resistance in the case of antimicrobial drugs."

respectful healthy dialogue. (See companion article on critical examination of COVID data.)

The above option ceases reliance on COVID vaccination and relies, instead, on the ingenuity and experience of the natural human immune system and supportive health efforts. A component of this option is to do "all of the little (but hugely important) things" to support our immune system's work. This includes attention to nutrition, exercise, emotional and spiritual health; correction of systemic socioeconomic and health care delivery problems; and reversal of environmental toxicities. In addition, efforts could be maximized to preventively treat early mild COVID before it evolves into severe disease.

This option would likely result in adequate natural herd immunity (which is likely to be superior to vaccine-induced herd immunity) and would likely nudge the SARS-CoV-2 virus towards gradually becoming less virulent and less transmissible, rather than more virulent and more transmissible. Ultimately, this option could reduce cumulative COVID-related hospitalizations, ICU admissions, and deaths, while also reducing fears, despair, confusion, angst, anger, polarization, extremism, and intolerance. It could be an instructive, empowering, and uniting process that restores civility and ushers in an era of altruism and healthy living that respects and nurtures the Human Race, all living things, and the earth itself.

Even if the Commission (and the public) conclude that the above hypothesis is not correct (or, at least not of significant practical concern), the Commission might, nevertheless, conclude that the mass vaccination campaign should be halted anyway — not because vaccination is driving development of increasingly worrisome strains; but because of legitimate, major concerns about the safety, efficacy, necessity, and wisdom of these vaccines. (See companion articles on vaccine concerns.)

If the Commission concludes that the above hypothesis is correct, there is one option that should be *avoided*, if at all possible. Namely, some virologists/vaccinologists have suggested that the best solution for a worst-case scenario (of vaccine resistance) would be to develop a new approach to vaccination that is more effective, more optimal than the current suboptimal vaccines — for example, development of vaccines that "educate the immune system" to mount a robust NK-cell attack against the SARS-CoV-2 virus. Such a plan may sound scientifically impressive and tempting but would lead Humanity even further away from wise reliance upon and support for the natural human immune system. But if we allow a worst-case scenario to evolve, we might have no choice but to go the route of NK-cell vaccines.

BOTTOM LINE

A good outcome to the COVID pandemic depends on widespread critical thinking, careful consideration and study of legitimate concerns, healthy public dialogue, quality data, and thorough honest reassessment of where we have been, where we are, and where we might go. If a change in course appears to be necessary and wise, it is not too late. According to their capacity, each person needs to do their homework and participate in respectful public dialogue.

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