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Editorial

The COVID-19 Vaccines that weren't

Hakim Djaballah*

Keren Therapeutics, New York, USA

***Corresponding Author:** Hakim Djaballah, Keren Therapeutics, New York, USA.

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"By failing to prepare you are preparing to fail" Benjamin Franklin.

"Immature poets imitate; mature poets steal; bad poets deface what they take, and good poets make it into something better or at least something different…" T.S. Elliot.

Twenty years ago, more than 50 initiatives began their search for the ultimate vaccine against the Severe Acute Respiratory Syndrome (SARS), few more joined to tackle the Middle East Respiratory Syndrome (MERS) in 2012. Many seem to have achieved proof of concept in animal models, but very few entered human clinical trials to assess safety and immunogenicity, and then the trail went cold until April 2020. After that, a new cycle of more than 100 new initiatives begun in an unprecedented race to develop a vaccine against the SARS-CoV2 virus causing the Coronavirus disease (COVID-19) as the world was witnessing a global pandemic spreading like fire from one country to another as never seen before. All because of bad decisions that allowed the virus to leave China with no country was prepared for what was coming.

None of the prior initiatives came close to develop a vaccine or address a simple question of what would be its main characteristics? In essence, 1) It should be safe without serious adverse effects, 2) provides active immunity with 5 to 10 years duration, and 3) protects from viral infection, re-infection, and viral colonization. Though their animal model studies demonstrated that various vaccine platforms were somehow safe and immunogenic to the extent of what their experimental design can capture, the vaccinated animals were found to be susceptible to viral infection in similar fashion to the unvaccinated group, and displayed significant disease upon challenge with the coronavirus.

It was well documented that at best, any developed vaccine against the SARS-CoV2 virus or other coronaviruses, would only provide partial protection in producing neutralizing antibodies with induction of cellular immunity, which could potentially protect the vaccinated from developing severe COVID-19 disease and avoid hospitalization. These vaccines will not provide any protection against viral infections and re-infections, and will likely increase potential incidences of re-infections in the vaccinated population. Nonetheless, several vaccine platforms (Table 1) were advanced reaching human clinical trials and resulting in emergency authorization use, for some; to have them deployed as of December 2020 to fight COVID-19, and later receiving full regulatory and registration approvals in many countries.

Since the time of Dr Louis Pasteur and his disciples, human challenge clinical trials have been at the heart of vaccine development and have been used to interrogate the efficacy of any vaccine in preventing infection by the pathogen in vaccinated human subjects; they have contributed critical knowledge that has helped the advancement of safe and truly protective vaccines. Though such trials can appear to be in conflict with the guiding principle in medicine to do no harm, their added value in the information to be gained should clearly justify the risks and ethics to the enrolled subjects. Although they are not a regulatory requirement for every vaccine in development, there are

Platform	Antigen	Cargo	Technology	Efficacy (%)	Company
	Single	Protein	Recombinant Spike	90	Nanovax, USA
	Single	Protein	Recombinant Spike	90	Medigen, Taiwan
Pasteurian	Multi	Protein + RNA	Inactivated SARS-CoV2	79	Sinopharm, China
	Multi	Protein + RNA	Inactivated SARS-CoV2	66	Sinovac, China
	Multi	Protein + RNA	Inactivated SARS-CoV2	93	Bharat Biotech, India
	Single	DNA	hAD26 expressing Spike	66	JnJ, USA
Viral Vector	Single	DNA	hAD26 expressing Spike	76	Astra Zeneca, USA
	Single	DNA	hAD26 expressing Spike	90	Indian Serum Inst., India
	Single	DNA	hAD26 + hAD5	91	Gamaleya Res. Inst., Russia
	Single	RNA	LNP delivery	95	Pfizer|Biontech, USA
mRNA	Single	RNA	LNP delivery	94	Moderna, USA
	Single	RNA	LNP delivery	48	CurVac, Germany

Table 1: *Platforms used for COVID-19 vaccine development.*

plenty of reasons as to why a regulatory agency may require the developer to conduct a "challenge-protection" study as part of phase 2 clinical trials to assess vaccine efficacy, setting the stages and follow up requirements for a larger phase 3 clinical studies to confirm both safety and efficacy in larger cohorts.

Though hailed as the most incredible scientific accomplishments of all times and during a global pandemic where many countries were under lockdown, the rapid design, production, and deployment of a variety of vaccine platforms to fight SARS-CoV2 (Table 1), including the use of novel technologies never tried and approved prior to this; such as mRNA and viral vector based vaccines encoding the viral spike protein. With the exception of the traditional Pasteurian platforms using whole inactivated virus, the rest of the platforms were single antigen vaccines focusing solely on the spike protein of the coronavirus, and its design based only on the Wuhan strain.

What had transpired during the various approval processes for all of these vaccines was the complete omission of the human challenge protection clinical studies as means to demonstrate that, beyond safety and seroconversion, these experimental vaccines offer protection against SARS-CoV2 infections; and in turn would stop viral transmission and propagation, thus the ultimate wish for ending the pandemic. It seems that regulatory agencies looked the other way for reasons that may be explained in the near future; though in some countries, they had received ethical approvals to run SARS- CoV2 human challenge studies. Therefore, approvals were decided based on 1) seroconversion as primary end points showing humoral protection producing neutralizing antibodies against the spike protein, and 2) a safety profile summing up all the observed adverse effects, but clearly insufficient for mRNA and viral vector based platforms due to their novelty and do require longer safety monitoring periods.

In a very complete contrast to these COVID-19 approved vaccines, experimental HIV vaccines developed by the giant pharma company Johnson and Johnson with their partner the National Institute of Allergy and Infectious Diseases (NIAID), formerly directed by Dr Anthony Fauci, failed to protect against infection by the HIV retrovirus, and as such, their developments were terminated as they failed to demonstrate the most critical function of the vaccine. With all the precedent coronavirus vaccine development data, one can only wonder why the U.S. Food and Drug Administration (FDA) did opt to approve them without this critical protection from infection by SARS-CoV2 as a primary end point within the clinical path to approval. It is also the reminder of another vaccine that had proven to be more of a Trojan

horse rendering vaccinated people much more susceptible to infection by the dengue virus; the developer of this vaccine knew ahead of time but ignored the facts just because it was registered in low income countries ravaged by dengue fever.

In an unprecedented way and never seen before in public health settings, decisions were made for a vaccination only policy on a global stage with a mission to inoculate the masses during an active ongoing pandemic. Such vaccination strategies that risk producing adverse outcomes in a given population could easily be defined with a clear stratification of who needs to be vaccinated and why?; and in view of a vaccine's partial efficacy, further raises questions of how its use might be combined with more effective control measures, and whether its worldwide use is warranted during an active ongoing global pandemic. Even regions could not be stratified as low-transmission, medium-transmission, and high-transmission terrains to help with the need for vaccination or just monitoring.

Emerging real world data on this vaccination only policy two years after it began, with well over 13 billion doses administered, suggest that it has done more harm than good to the world population; for sure, it had not halted the pandemic as was promised by our political leaders and their scientific and medical advisors who said "…get vaccinated and life will return to normal…"; alas it has not yet. Surprisingly, it seems that the more we vaccinate, the more new cases are recorded; on par with their partial efficacy but providing evidence that they may well be rendering vaccinated people much more susceptible to SARS-CoV2 infections. Instead of cautiously pausing the vaccination efforts and perform interim reviews, decisions were made to double down on these partially effective vaccines by introducing scientifically unfounded and invalidated principles of booster doses of the same vaccine within 3 - 6 months intervals. Never seen before that large pharma companies would provide, in support of these booster shots, mediocre data based on a handful of individual sera analyzing the neutralizing activity of antibodies. This was another unprecedented deviation from quantitative high scientific and ethical research to a politically and revenue driven one.

In summary, more dangerous and criminal than fraud in science is its politicization, with dire consequences on the lives of many as we are witnessing, with several million deaths and many more presenting with new health issues. These vaccines may have saved lives from severe COVID-19 disease; they had no impact on ending the pandemic and may well be the cause of its durability. Therefore, since these vaccines are unable to stop the spread and kill the virus, it would have been more accurate to refer to them as "prophylactic" treatments rather than calling them "vaccines", especially in view of the additional booster doses. A multi-component retrospective study is therefore warranted to assess both damages and benefits of this vaccination only policy using partially efficacious vaccines. One question remains unanswered: What would the pandemic landscape without any vaccine intervention have looked like in terms of numbers of deaths and infections?

Conflicts of Interest

I declare no competing interests.

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