Vaccines, Germs, and Knowledge*

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Abstract

Vaccines for COVID-19 have led to questions, debates, and polemics on both their safety and the political and geopolitical dimension of their use. We propose to take a step back on both the history of this practice and how current theories in immunology understand it. Both can contribute to providing a rational assessment of COVID-19 vaccines. This assessment cannot consider vaccine as an isolated procedure, and we discuss its intergradation with the broader question of knowledge and politics in the COVID-19 pandemic.

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Vaccination is singular because it has a collective aim - sometimes even the eradication of a human pathogen - and, at the same time, it involves a medical procedure on individuals who are without the disease of interest. In that regard, vaccination meets the question of trust straightforwardly. However, its political ramification is not limited to the point-wise use of vaccine; its theoretical background directly relates to our relationship with other animals on the one side and microorganisms on the other.

1 A very brief history of vaccines

Domestication has led to the promiscuity of humans and several other species. Living together means regularly exchanging microorganisms such as worms, amoeba, bacteria, and viruses. Microorganisms can jump from one species to another, especially when the hosts are relatively closely related evolutionarily and, therefore, similar physiologically. The domestication of mammals entailed the emergence of new contagious diseases for humans. Moreover, sedentary lifestyles led to an increase in population density, and the latter determines the odds for an obligatory parasite, like a virus, to sustain itself in a population.

One such virus leads to smallpox. Smallpox is a dreadful disease with a 30 to 50% death rate, leaving survivors scarred for life. Early archaeological and written records of smallpox have been found in ancient Egypt, then China. Trade,

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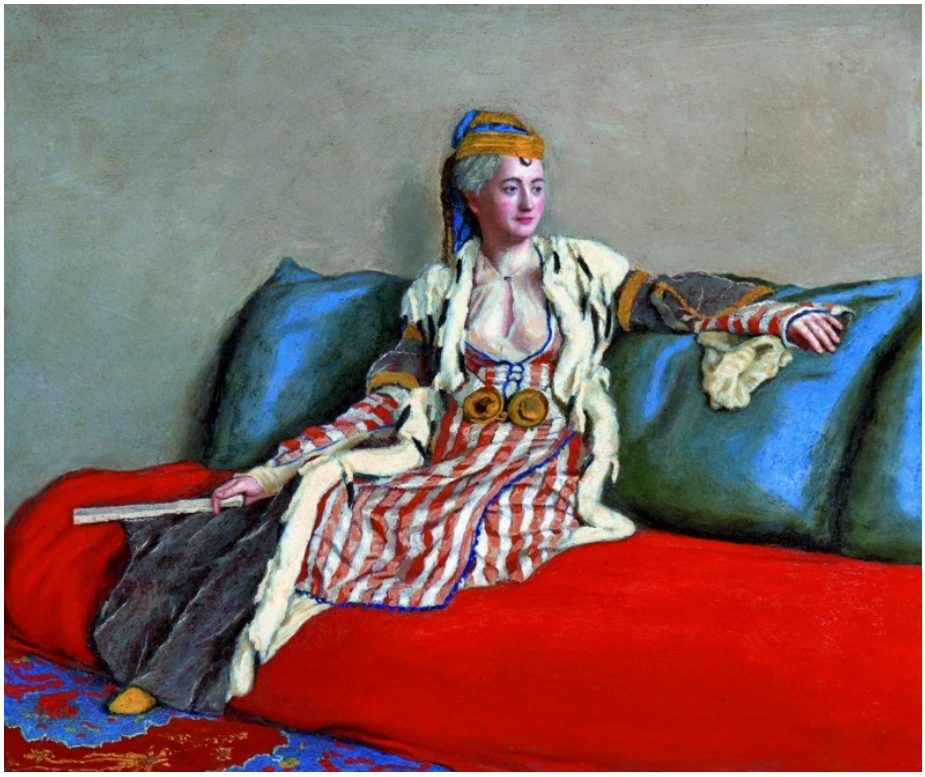
crusades, and, later, colonization carried the virus around the world, and it was, among other things, central to the collapse of Amerindian civilizations, both by accidental and purposeful contaminations. The human variant may come from cow strains - Amerindian civilization did not domesticate cows, which explains why they were more vulnerable to smallpox than Eurasian and African populations. In any case, variants of the virus have elected cows, camels, monkeys, and, of course, humans as their hosts - we will see that this point is critical to the invention of vaccines.

Such a dreadful disease led to the emergence of a practice called inoculation. This procedure is daring; it requires exposing subjects to a somewhat weakened puss sample from a sick person. The outcome was fewer chances to contract the full-fledged disease; however, in one or two percent of the cases, inoculation led to death. This practice probably emerged in China and propagated over the silk road. Some evidence suggests that it may have also appeared independently in Africa. There are also claims of Ayurvedic practice of inoculations; however, these claims may stem from a British propaganda strategy in the early XIXth century to favor adopting the practice.



Lady Montagu in Turkish dress, Jean-Étienne Liotard, Circa 1756; Image credit: Wikimedia Commons

In any case, in the early XVIIIth century, inoculation was practiced in Istanbul and witnessed by lady Mary Wortley Montagu, the British ambassador's wife who suffered personally from the disease. She applied it to her son and brought the procedure back to England. Needless to say, a Turkish folk practice advo-

cated by a woman, even an aristocratic woman, met with some resistance; however, the crippling effects of smallpox on society led it to widespread adoption nevertheless. Inoculation raised debates of many kinds, including a mathematical debate between Bernoulli and D'Alembert, on the rationality of inoculation based on the emerging theory of probabilities, a theory initially directed towards gambling and trade boat insurances. This debate already involved evaluating the benefits of such a practice quantitatively by counting life expectancies and not just the deaths attributed to the procedure and the disease. Nevertheless, both participants advocated inoculation in practice (2).

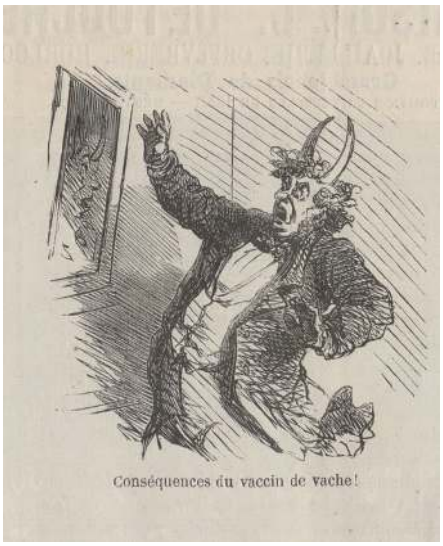
Edward Jenner introduced significant progress into this practice. He observed that milkmaids did not contract smallpox. Therefore, instead of using human samples, he used bovine samples, called vaccines (from the Latin *vacca*, cow). The cow variant of the disease was better for inoculation since it was largely benign for humans, reducing the inoculation's deadly side effects. Nevertheless, it was also met with resistance, raising fears of minotaurization - the putative partial transformation into cows.

The step further was taken by Louis Pasteur. Epidemics were conceptualized in Europe as spread by vitiated air, a perspective called miasma theory. This idea notably led to the striking masks of plague doctors, filled with aromatic herbs intended to purify the inhaled air. Pasteur's continuous drive was to show that germs were required for fermentation and similar processes, leading to dismiss the concept of spontaneous generation - the notion that full-fledged living beings appear spontaneously in the right condition, for example maggots in dead animals. In the case of diseases, he contributed to germs theory, the notion that microorganisms originate a category of diseases - infectious diseases. With this framework, he generalized the process of vaccination by attenuating microbes. He experimented firstly on animals and then humans in the case of rabies. The generalization of vaccination was an outstanding breakthrough for public health. In 1977, a century later, vaccination reached a symbolic peak with the global extermination of smallpox by an international effort coordinated by the World Health Organization.

Still, vaccination had its failures. Let us mention two very different ones. First, in 1930, contaminated vaccines against tuberculosis led to the death of 72 children in Lübeck, Germany. Despite the investigation and prosecution that followed and traced the problem to a laboratory mistake in Lübeck, it took 20 years for this vaccine to be fully acknowledged as harmless. Second, despite many efforts, the changing nature of HIV still escapes vaccine development. Therefore vaccines are not a universal response to infectious diseases. Developing them may be straightforward or, on the opposite, extremely challenging depending on the pathogen.

2 Immunology

An uncomplicated observation, done already in antiquity, was instrumental to the emergence of vaccination: survivors of an epidemic would not contract the same disease, at least for a while. This observation led to the notion of immunity, from the Latin "immunis": exempt, free, not paying a share. Inoculation and then vaccination are methods to jump-start this phenomenon without - hopefully- contracting the disease *per se*. The notion of immunity and the



Cham, « Croquis », Le Charivari, 3 April 1870. Image credit: Gallica (BnF).

body of works on infectious diseases founded the field of immunology. Building on Claude Bernard's concept of "milieu interieur" and the practical application of fighting pathogenic germs, immunology started with a sharp distinction between the inside and the outside and the self and non-self. The postulated immune system's function derived from the immunologists' social function, fighting pathogens invading human bodies. Other medical practices consolidated this idea, notably organ transplants' procedures, where a significant difficulty is graft rejection. It is worth mentioning that the latter phenomenon is far from universal; plants are more flexible than mammals, and grafting different species of the same genus together does not trigger a pathological immune response in them. The perspective of fighting against pathogen invading the "milieu interieur" also led to systematic hygiene practices intended to eliminate germs preventively.

The scientific acme of the self/non-self contrast is the clonal theory developed by Frank Macfarlane Burnet. This theory's rationale is very close to the modern synthesis in evolutionary biology and the automatic optimization of markets in neoclassical economics. They are all theories of spontaneous "order" without complexity or failures. (3) Burnet's theory posits that lymphocytes' proliferation includes a process of generating diversity in their ability to recognize antigens (molecules triggering an immune response). Then, lymphocytes undergo a process of positive selection based on the antigen they recognize. When meeting an antigen they recognize, lymphocytes proliferate. After the infection, a part of these lymphocytes would remain sleeping; thus, an acquired immune response against these antigens' carriers can emerge. An addendum to this theory is that lymphocytes undergo a negative selection process during their maturation in the thymus. This process would eliminate lymphocytes recognizing the self, thus leading to an immune system that would not attack it, thus providing an immunological definition of the self. This theory also separates the so-called innate and acquired immune responses strictly. The innate

immune response corresponds to the generic recognition of pathogen molecules retained during evolution, while the clonal theory would explain the acquired immunity of jawed vertebrates.

The clonal theory builds on empirical evidence. First, lymphocyte maturation involves random DNA recombinations, leading to the generation of a diverse immune repertoire. Second, lymphocytes mature in the thymus, where a specific process leads to the random production of proteins, generating a body's chemical image. A significant portion of the lymphocytes indeed does die in the thymus, suggesting a kind of selection.

The theory justifies the emergence of spontaneous order; however, this rationale is overly simplistic, like the theories of spontaneous optimization in economics and evolutionary biology. Let us mention a few of its shortcomings.

Some vaccines include living microorganisms; others called inactivated vaccines, include only chemicals from the pathogen. The latter often require an adjuvant to be potent. From the perspective of clonal theory, this does not make sense: presenting antigens to the immune system should be sufficient. An alternative theory, the "danger theory," has been proposed by Polly Matzinger to accommodate this phenomenon, among others (4). The central idea of this perspective is that cells under stress produce chemicals that trigger the immune system. Therefore, a vaccine that would not stress the body would be utterly inefficient - and therefore inactivated vaccines require an irritating adjuvant. Conceptually, this framework blurs the distinction between the self and the non-self, which both are no longer well defined from the immunological perspective. Instead, stress is central, and so is the coupling between innate and acquired immune responses, that is to say, the coupling between evolutionary and ontogenetic memory scales.

Another major shortcoming of the clonal theory derives from the microbiome, our symbiotic microorganisms, notably those living in the guts. Lynn Margulis already showed in the sixties how the integration of a symbiont was a key factor in evolution, namely bacteria that became mitochondria, a critical part of our cells. In the last decades, technological progress in gene sequencing enabled scientists to "see" the microbiome and, thus, to assess its role. Earlier accounts seriously underestimated this role; now, biologists consider that the microbiome constitutively participates in development and physiology. Biologists like Scott Gilbert posit that we are holobionts, a composite of cells from different origins instead of only or primarily cells stemming from the egg's clonal proliferation (5). These discoveries further shatter the self/non-self opposition; here, the immune system and the microbiome become an integrated system, where both parts regulate each other. They may also enter pathological relationships, leading to Crohn's disease, allergies, and other pathologies. Among them, the connection between the microbiom and neurodegenrative diseases such as Parkinson disease is a very active field of research. This new perspective leads to a critical view of hygiene. Being surrounded by a micro-organic desert disrupts our historical milieux and would disorganize our immune system development. This reasoning contributes to explain the epidemiological increase of the diseases mentioned above (6).

Other theories to accommodate these observed discrepancies with the clonal theory are worth mentioning briefly. Building on the notion of cognition, Thomas Pradeu and others developed the notion that the immune system detects changes, not an absolute state of affairs. This notion has been called the discontinuity

theory (7). Like the danger theory, it accommodates better both the microbiome and the vaccine adjuvants. Another framework emphasizes the relations between lymphocytes, leading to mutual regulations in a network called the idiotypic network. This perspective builds on an observation that is non-sensical from the perspective of the clonal theory. In the thymus, lymphocytes with high avidity for proteins from the self are selected against – which makes sense for the clonal theory. However, lymphocytes that have insufficient avidity towards these proteins are also selected against. In other words, auto-immunity is not just a pathological condition; it is a constitutive part of the immune system's physiology. In the idiotypic network model, lymphocytes collectively regulate each other, and lymphocytes disconnected from the network stop proliferating and thus disappear (8). This theory explains another discrepant fact. If we prevent lymphocyte proliferation, the immune system loses its memory. Therefore, contra the clonal theory, the lymphocytes that carry the immune memory are not merely sleeping; they are actively proliferating, possibly under the idiotypic network regulation.

Even though these discrepant facts are mostly consensual among immunologists and acknowledged as both facts and discrepant, they did not trigger a broad change of theoretical framework - namely, giving up on the self/non-self distinction and proposing a new understanding of what biological immunity is about. It is not the place here to discuss why, and a special issue of Philosophy Worl Democracy will address the state of theorization in current sciences. Let us mention that those reasons include the insufficiencies of alternative theorizations and the lack of theoretical fluency of most biologists. However, it is worth remarking that anti-vax movements build on theoretical weaknesses, notably the adjuvants whose role is mysterious from the clonal theory's perspective.

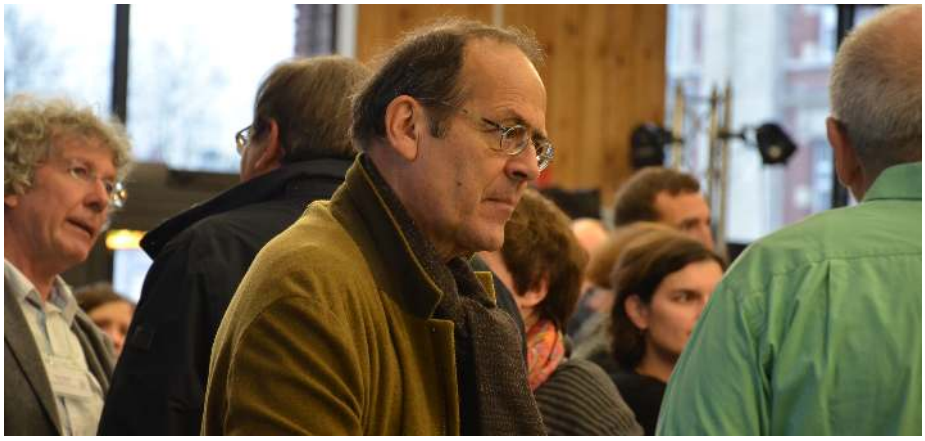
Let us also mention that, in immunology, theorization and understanding encounter a difficulty common in biology: concepts do not integrate well together because of the theoretical mix of natural history and relational perspectives (9). Biologists may define immunology by the biological function: for example, regulating microorganisms and possible parasites. Then, for example, some sea slugs display a surprising and somewhat extreme immune response when they rip their head off to get rid of a parasite-infested body, as recently discovered (10). CRISPR-CAS9, famous for its technological use in gene editing, also performs an immune function in bacteria.

Once the function is defined, biologists identify parts that play a specific role in this function, describing the immune system. However, what these parts do does not fit precisely the function. For example, macrophages hunt bacteria down; however, they also phagocyte (eat) "normal" dead cells - a process entirely disconnected from the question of parasites. Lymphocytes that strongly recognize molecules generated in the thymus based on the organism's DNA are selected against, which would define the self; however, many molecules of the body are generated by the microbiome; therefore, this perspective is partial. Living beings are not neatly organized like an ideal administration or machine, with parts performing only specific functions. Instead, they changed in evolutionary history, and the ability to generate novelties and the subsequent lineage's survival are the only strictly limiting factors of these changes.

Moreover, a central concept of biology is the distinction between homology and analogy - a distinction based on historical reasoning. Homologous body parts come from the same evolutionary origin, like human and cat limbs.

By contrast, analogous parts may look alike and perform a similar function, but they appeared independently as insect and bat wings did. The field of immunology alternates between the study of homolog parts and analog ones, which complexifies its object's nature. The theories mentioned above only make sense for homolog immune systems, namely mammals immune systems, because they do not embed the historical and, therefore, partly contingent nature of the immune system's organization. In other words, they typically investigate common aspects of mammals' immune systems and some variations of these common aspects. For example, the self/non-self distinction only makes (limited) sense for mammals' acquired immune system (the notion can be extended to the jawed vertebrates at best).

By contrast, if we start again from the immune function, humans display particular behaviors that contribute to regulating microorganisms with greater or lesser efficiency, such as using plague doctor costumes, surgical masks, and vaccines. In other words, somatic functions get performed or complemented by artifacts in a process that Bernard Stiegler (11), building on Lotka (12), called exosomatization. From this perspective, vaccines are peculiar; they contribute to providing an efficient biological response at the first exposure to the genuine pathogen, somewhat like the innate immune system. However, this response is possible thanks to technics instead of biological inheritance; and it depends on exosomatic memory instead of biological retentions (in particular DNA sequences).



Bernard Stiegler in 2014 Lamiot, Creative Commons Attribution-Share Alike 4.0 International

However, in Stiegler's thought, such artifacts are pharmaka, simultaneously poisons and remedies, and require knowledge to be both shaped and used in less toxic ways. Knowledge, here, should be understood in the broad sense; it includes academic knowledge as well as practical know-how.

3 Knowledge, vaccines, and COVID-19

Let us now discuss how the question of knowledge and vaccines meet in the case of the COVID-19 pandemic. To address this question, we will focus on the case

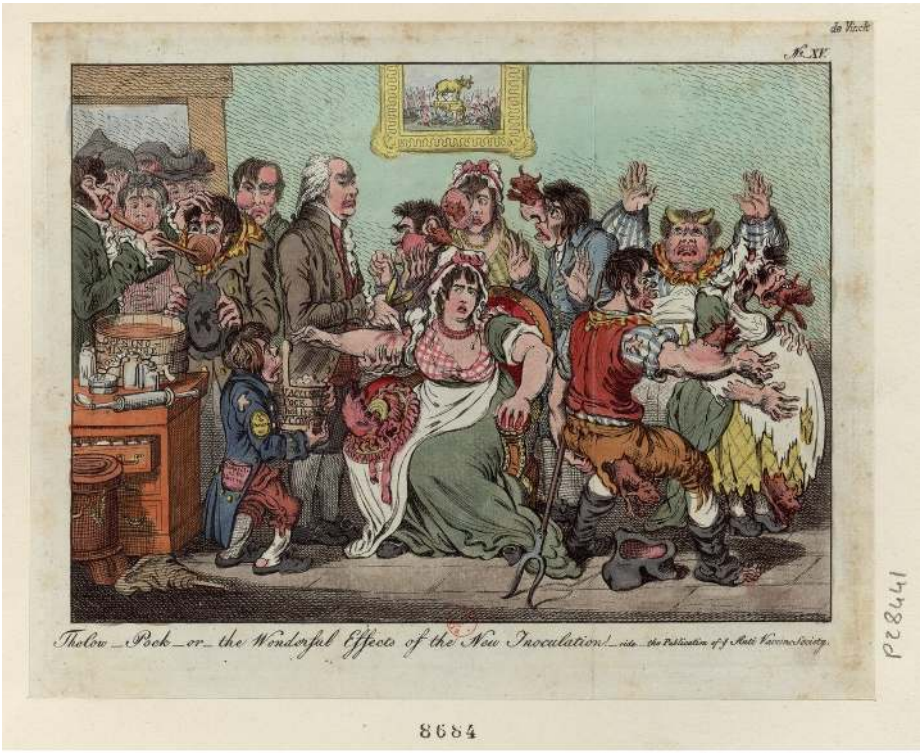
of France that we know better. Some of its characteristics seem to represent other western countries well, especially European ones, despite specific twists and turns.

Let us begin with one of those. The French president, Emmanuel Macron, firstly reacted to the pandemic by stating that "we are at war." Philosophers and medical doctors alike have rightfully criticized this attitude; however, two of its ramifications have not been discussed as such.

The US senator Hiram Johnson famously asserted that "the first casualty, when war comes, is truth." Here, truth need not be understood in a robust philosophical sense but by opposition to duplicity and, later, its industrialization as propaganda. The French government used several rather short-lived lies to escape difficulties, such as masks or testing capacities shortages, and it endorsed a normative role on truth and practical rules. More importantly, policies systematically used one of the newest propaganda methods, nudging, to shape people's behavior, as emphasized by Barbara Stiegler (13). Nudging is a method to bend behaviors without the subject knowledge and used by applications such as Über to orient drivers' behaviors, provided that they are not employees; that is, they are not in a relation of contractual subordination. Nudging is more broadly associated with libertarian paternalism (14). By contrast, critics emphasize the French government's incapacity to capitalize on the inhabitant's knowledge and capacities and, a fortiori, to promote their emergence. Understandably, based on this poor epistemic relationship, the government's words on vaccines do not carry much weight. Simultaneously, in the last decades, repeated scandals have crippled the trust in the pharmaceutical industry and its scientific collaborators. Here, we cannot help but recall Kant's concerns on lying being the downfall of speech itself.

The war paradigm's second ramification is that wars are periods of technological acceleration, where designs produced earlier enter industrialization, sometimes with shortcuts in their assessments. In the COVID-19 pandemic, this perspective is very relevant, as exemplified by the notion of a screen new deal coined by Naomi Klein (15). The use of remote conferencing could feed big-data systems development. Thus, the pandemic provides a technological alternative to digital surveillance as a data source. The technological acceleration is also very relevant for the vaccines themselves. Indeed, the first vaccines to appear on the market are a new kind of vaccine, called RNA vaccines.

Interestingly, these vaccines come from the technological lineage of attempts toward gene therapy. One of the shortcomings of gene therapy is that they trigger an immune response. This fault led to the idea of using these technics for vaccination. Let us briefly recall that DNA are long-lasting molecules transmitted from one generation to the next and are a crucial medium of biological heredity. By contrast, messenger RNAs are short-lived, unstable molecules that are an intermediary between DNA and proteins in cellular protein production. The principle of RNA vaccines is then to inject RNA into cells so that the cell itself produces some of the pathogens molecules (let us recall that classical vaccines are parts or weakened versions of the pathogen). The so-called central dogma of molecular biology is a strangely named theoretical assumption stating that "information" flows from DNA to RNA and then from RNA to protein and never back. Following this dogma, RNA vaccines would not impact DNA. A caveat is that this dogma dates back to the sixties and has since been proven wrong. Nevertheless, being wrong in general does not imply that it is wrong in



The Cow-Pock-or-the Wonderful Effects of the New Inoculation!-James Gillray 1802

this particular case. Like in the case of immunology, the lack of recent theorization to accommodate discrepant facts prevents an accurate assessment of RNA vaccines' effects.

Empirical investigations partially compensate for these theoretical shortcomings; however, these investigations have several weaknesses. First, they are very limited in the time window considered - for obvious reasons. A substantial empirical investigation strategy could have partially compensated for this shortcoming with animal models (their life cycles can be far shorter than humans); however, no such program has been organized to our knowledge. Pharmaceutical companies have just organized clinical trials to meet standard regulation criteria, and public research has been mostly confined to the usual circuits of grants proposal, sometimes just hastened. In other words, there was no political will to know what we need to know, a kind of *abulia sciendi* of the political establishment concerning these matters. This situation can be contrasted with the French minister of research's recent attempt to launch an extensive investigation on "Muslimo-leftism" (islamo-gauchiste) in academia - a request met with scorn by academic representatives of all stations.

Second, controlled clinical trials are limited in the diversity of cases encountered (16). The latter limitation is universal to all clinical investigations of new drugs or procedures, so they require a follow-up to understand possibly somewhat rare side effects - the use of a drug in the general population is the fourth

stage of clinical trials from an epistemic perspective. The case of COVID-19 RNA vaccines is particular since it involves exposing huge populations to an entirely new compound in a short amount of time. The odds of long terms detrimental effects seem low, but the exposed population is enormous. In this discussion, as emphasized by Canguilhem, we should not forget that medicine, here extended to public health, is an art and not a science. Judgment is required to assess the benefits and the risks. To mitigate the latter, it seems sensible to use a diversity of vaccines at the population level and, for young people, to adopt more classical vaccines than RNA ones.

Using a diversity of vaccines has another benefit. SARS-Cov-2 is far from static; it has many available hosts to reproduce in, and biological reproduction goes with variations; thus, the virus diversifies. Concerns about variants escaping a vaccine can be mitigated if we use a diversity of vaccines, especially if they build on different aspects of the virus. Biological uniformity is highly vulnerable to pathogens, while diversity creates barriers in the population, and if a strain escapes a vaccine, only the part of the population that has used this vaccine needs to react.

This rationale is not limited to the case of vaccines; it is relevant at the ecosystemic level. Biotic homogenization due to biodiversity loss and intensive animal farms greatly facilitates the emergence of infectious diseases, and they do emerge at an accelerated rate (17). The field of disease ecology has established this point before the emergence of COVID-19, and it is probably part of the SARS-COV-2 appearance explanation. In other words, biodiversity contributes to constraining potential pathogens outside the body, as the immune system does inside the body. Moreover, as mentioned in the previous section, our immune systems are disrupted by the changes in our milieux, probably leading to the observed epidemiological increase in allergies and autoimmune diseases, among others (6). Vaccines only induce somatic retentions that lead to a faster response to the targeted pathogen. They contribute to the interplay between humankind and microorganisms in the Anthropocene context; however, they are not the more general care that our immune systems and ecosystems require. Discourses that polarize the debate between irrational anti-vaccine positions and putative rational pro-vaccine positions without including the above considerations are characteristic of an instrumentalization of sciences. They follow their results when they are in line with the establishment - the deployment of technologies is usually welcome - and ignore scientific conclusions when they have more subversive ramifications for the current social and industrial state of affairs. The same critical view is relevant to vaccine patents that prevent a worldwide vaccine strategy, unlike for smallpox. Again, the unbalanced use of science contributes to the distrust that disrupts its contribution.

Moreover, unlike smallpox which affected equally all social groups, severe cases of COVID-19 are particularly prevalent among underprivileged groups. Richard Horton argues that COVID-19 is not a pandemic but a syndemic, a disease where biological and environmental causes are interwoven (18). Comorbidities to COVID-19 do not stem simply from poverty; instead, they stem from the preexisting pandemics of non-communicable diseases. A fair part of the latter derives from unhealthy commodities for which "the vectors of spread are not biological agents, but transnational corporations" (19). More broadly, consumer capitalism went with the destruction of practical knowledge and its replacement with prescriptions following the industries' needs: the consumption

of its productions. Amartya Sen, frequently quoted by Bernard Stiegler, emphasized that male life expectancy in Bangladesh during a famine was higher than in Harlem and coined the concept of capacity to understand the Bangladeshi population's resilience, a form of practical knowledge (20).

Taking all these elements into account, COVID-19 is more a symptom than a disease, and vaccines are symptom-relieving drugs, not a cure. The XXIst century will be complicated, scientists say. The damaging epistemic clumsiness of scientists, populations, and political leaders alike is characteristic of the response to COVID-19; to do better, theoretical accuracy and a new alliance of scientific and popular knowledge is required.

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