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WHAT DARWIN COULD TEACH US TODAY ABOUT MODERN VACCINES AND THEIR HEALTH POLICIES

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INTRODUCTION

Like Molière's bourgeois Jourdain, who realized he had been speaking prose for forty years without knowing it, we have been talking about Darwinian evolution since the pandemic began and in increasingly stringent ways in the past year. Though usually, it seems, without our even realizing it (2). The emergence and spread in different epidemiological ecosystems of new variants of SARS-Cov-2 were certain facts, like the rising of the sun. So certain that mathematics, so abused to make daily and often disproven predictions of epidemiological changes with increase/decrease of cases or deaths, was not needed. The recurring questions are whether the new variants are more efficient in replicating, transmitting, or causing damage to the host, or if they will escape, as changed in antigenic conformations, immune responses trained naturally by infection with the virus or artificially by vaccines. These are questions pertaining to Darwinian immunology and vaccinology. The topic also concerns the hot debate on the origin of SARS-CoV-2, which at times takes on the profile of a confrontation between those who think that natural selection, with favorable conditions at its disposal, achieved the changes necessary to infect humans, and those who instead think that some artificially estimate of probability of a phenotypic variant (furin cleavage site) is sufficient to resort to a sort of intelligent design (1).

DARWIN AND PASTEUR

In the tradition of evolutionary or Darwinian medicine, Darwin is contrasted with Pasteur, because the latter was, along with Claude Bernard and Robert Koch, the lord of the "proximate or immediate causes" of diseases, those that can be studied experimentally in the laboratory as pathogenic parasites, while Darwin is the master of the "remote or evolutionary causes" of biological changes, those that are discovered by studying with observational, experimental/mathematical methods the natural history of living species, *i.e.* how and why their phenotypic traits and underlying genotypes/pools of genes have changed in the course of descent (3). Pasteur's ideas and methods in-

vented scientific medicine and generated the ambition to eliminate or control all microbial causes of disease. Except for the remote ones, *i.e.* due to the fact that the genome from which human phenotypes develop has been selected in the environment of evolutionary adaptation, accumulating defects and predispositions that were advantageous at the time and that perhaps one day we will be able to correct only with more advanced technologies than the current ones of genomic editing. In short, Pasteur allowed us to imagine and build vaccines or drugs, while Darwin explained, with the theory of natural selection, that not even with the means of medicine we could imagine realizing the best of all possible worlds.

Moreover, Darwin could be defined as a layman, who followed the developments of microbiology, while Pasteur was a religious conservative, and had no sympathy for the theory of evolution, which resonated with him as the aberration of believing that we are descended from monkeys. In the late nineteenth century, some French microbiologists argued that in fact Pasteur was to medicine what Darwin was to natural history, in the sense that the techniques aimed at developing transformed pathogenic strains to be used as vaccines applied the same principles as Darwinism or in some ways were artificial selection. This was not the case. The idea that guided Pasteur was that the culture medium of microorganisms induced hereditary changes in Lamarckian ways (Darwin too believed in the heritability of acquired traits but not in a drive toward change in an adaptive sense) and caused new species to emerge with attenuated virulence. Ready for vaccines. The French microbiologist thought that immunity had no independent physiological basis but was due to the mere depletion of nutritional factors in the host, after the pathogen had lodged there leaving the host alive (5).

The modern concept of vaccination, shepherd, is not related to Darwinism, because it is inscribed in an idea of immunity as a passive phenomenon and despite some late nineteenth-century physiological models of immune response that sensed the active and dynamic nature of the phenomenon, we had to wait until the fifties to begin to understand and then demonstrate that immunity depends on a complex genetic-molecular architecture, which governs the dynamic or cytokines-mediated interactions of cell populations with different roles and where the specificity of responses is governed by clonal selection. An idea, that of clonal selection, that Frank Mcfarlane Burnet, in the late fifties, directly linked to the Darwinian idea of natural selection.

Vaccine makers have long been artisans, rather than scientists, and they did not design them based on a controlled knowledge of immunity but arrived at the result by trial and error. The logic of invention, as it happens for many innovations and according to Karl Popper also for scientific theories, is still partly evolutionary.

ORIGIN AND TECHNOLOGICAL EVOLUTION OF VACCINES

Vaccines are an invention of human ingenuity and descend from observations and magical ideas (4). Officially the first to observe during the so-called Athens' plague of 430 b.C. that people who recovered from an infectious disease did not get sick a second time (immunity acquired naturally) was Thucydides. Likely, the phenomenon had already been observed, but the context of the "plague of Athens", where people were crowded and the disease had a rapid clinical course as lethal or healing, facilitated the description. As well as we can imagine that since antiquity it was realized that there were milder forms of a specific contagious diseases that protected from other serious forms, for example Alastrim due to the species variola minor that immunizes against classical human smallpox, caused by variola major. The first form caused a mortality of about 1%, compared to 30%. The widely held magical principle that like cures like (similia similibus curantur) was probably an early intuitive interpretation for the naturally observed

effects. Artificial immunization, using Alastrim, or variolation, according to Joseph Needham was practiced in China around the year 1000, and in 1720-22 it came to Europe. It was supplanted by Jenner's vaccinia, the cow's adapted pox virus, in 1796 (banned in the UK in 1840) using cowpox.

The evolution of vaccines and technologies is a well-known story that has no logic or finalistic sense. Like an evolutionary process. After Jenner and the smallpox vaccine, which protected against human smallpox by cross immunity, came in 1885 the first human vaccine with live attenuated agents (against rabies): both before the identification of the causative agent of the disease. They were very "dirty" vaccines, in the sense that they could transmit other human or animal pathogens or cause adverse reactions as well as the were used without safety and efficacy controls. The political, social and health expectations and logics were very different.

Since the first typhoid vaccine in 1896, the discovery of the agent has always preceded the creation of the vaccine, with varying timescales, ranging from almost a century for the meningococcal meningitis (1887-1970/5) and Haemophilus influenzae (1892-1985) vaccines, to a few months as in the case of the 1957 influenzas' vaccine or SARS-CoV-2 vaccine. Social pressures due to the impact of the disease, technological availability and biological characteristics of the pathogen are the variables that influence vaccine development. The first inactivated vaccines, after the one against rabies, were against plague, cholera, and typhoid fever, while in the twenties toxoids (which teach the immune system to recognize bacterial toxins) against diphtheria and tetanus entered the field, followed twenty years later by the first polysaccharide vaccine against pneumococcus. After a series of live attenuated vaccines in the sixties, of great health impact (polio, measles, mumps, and rubella), came the first vaccine made up of subunits (molecular components of the pathogen), against influenza and other viral infections, among which a few against SARS-Cov-2 has been approved in Western and Eastern countries. In the mid-1980s recombinant DNA technology was used for the hepatitis B vaccine, and subsequent recombinant vaccines up to those carried by viral vectors (such as the adenovirus used to vaccinate against SARS-CoV-2). In the same decade, conjugated polysaccharide-based vaccines (anti-H. influenzae b, anti-meningococcal C, anti-meningococcal ACWY) entered the scene. The rotavirus vaccine was the first vaccine genetically reassorted to enrich the antigen profile. Today we have the first approved nuclide acid vaccines, namely mRna vaccines against Covid-19.

UNCERTAIN SOCIAL FORTUNES OF VACCINATIONS

Vaccines have improved dramatically in terms of safety as their approval has gone through clinical trials since the 1960s (4). Adverse reactions are less severe or more predictable, and incidents due to recovery of virulence from live attenuated vaccines with fatal outcomes less likely. Why is it that, if they are safer, prejudice against vaccinations is so persistent or growing? This is normal: we cannot change our perception of risk based on correct information alone. Human decision making and judgment depend on or and controlled by heuristics and biases that were acquired by natural selection to survive in EEA, and to decided, in some situations, we tend to ignore true information and prefer false ones. A consequence of Darwinian evolution.

It does not appear that variolation caused a rejection in Asian and African societies that practiced it, while when it arrived in Europe and North America in 1721-22 quite a few theologians, doctors and Enlightenment philosophers opposed it. Among them, Jean Jacques Rousseau and Immanuel Kant on grounds of unnaturalness and ethics. Smallpox vaccination was also accepted in the compulsory form in several continental countries, less democratic, but not in England invested

by liberal ideas. For over half a century, the vaccination had to face in Britain with social protests, which depicted propagandistically the inoculation as an interference in personal freedom and a physically disgusting act, a source of threat to human life. The rejection or hesitation towards vaccination, which could almost be understood in the nineteenth century since the material and the ways of vaccination were quite disgusting, has re-emerged in recent decades with preponderance throughout the West, for psychological reasons that probably remain the same.

Many explanations have been given for the aversion/hesitancy to vaccination, some of which invoke the fact that our minds have not evolved to trust people we don't know (doctors, or an abstract entity like the state) to tell us that there might be some minimal risk in vaccinating. If we do not study statistics, which were not taught by natural selection or education in the Pleistocene, we estimate risks incorrectly. Moreover, propaganda against vaccines still recruits the emotion of disgust as a form of contamination; disgust that as cognitive psychologists show served evolutionarily to defend us from parasites, by nowadays woks to associate vaccines with a danger. Paradoxically, the disappearance of parasites as pervasive threats has allowed vaccinations, which introduce something foreign into healthy people and imply a belief on trust that they are safe and protective, to be perceived as dangerous, that is, as polluting practices. Perhaps the best way to counter anti-vaccinism, at least in case of uneducated or emotionally orientated people, is to appeal to the innate origin of distaste for disease and the disfiguring and lethal effects that infections cause (6).

VACCINES AND MICROBIAL EVOLUTION

Since last spring, the question has been whether and when SARS-Cov-2 will attenuate its contagiousness and become symbiotic with humans, i.e., whether it will evolve into a run-of-the-mill cold virus. No one can say, although it is possible. One of the characteristics of Darwinian phenomena is that the variations that change the phenotype of an organism, therefore also of a virus do not arise with the *purpose* to make it "better" or optimize, therefore for example more contagious, virulent, pathogenic, etc. or all the contrary. They emerge at random, and the fact that they preserve and exhibit specific phenotypic traits depends on the replicative advantage (natural selection) in the environment in which they are found. Full-stop. Pandemic evolution is going its own way, in defiance of the human presumption that we can make predictions or know what should be done to bring it under control. This doesn't mean that nothing should be done, but that perhaps we should also think about maintaining the principles and values we value in our societies, and not put them at risk to chase a virus that is much more efficient. The virus, multiplying in different ecological contexts (Brazil, South Africa, India, immunodepressed British patients, children, *etc.*) and thus facing different selective pressures, emerges in the form of different variants. We certainly do not know them all, since the number of sequenced genomes at the planetary level is impressive but also negligible.

The question is therefore whether the new harmful variants will be blocked by the approved vaccines or by those coming, and whether the vaccines, as will be the case for some, which do not have complete efficacy, will favor the evolution of strains that survive, that is, whether they will become benign, or whether there will be a selection in favor of virulence. The first answer is easy: it depends on how the variants are changed at the level of epitopes (antigens) recognized by the immune system. And it is not a serious problem: if the current vaccines lose efficacy, the information to be sent to the cells can be changed to make them express new immunogenic epitopes. The platforms set up over the past year by the companies that make the vaccines, in particular those at mRna, are flexible enough to update them all the time. As we already do

every year, albeit with different technologies, for the flu vaccine.
The second question does not have a precise answer. We have long wondered if there is resistance to vaccines, as to drugs, and if so, how it evolves. In fact, it is not frequent. Resistance to drugs, for example antibiotics or anticancer drugs, typically emerges soon after the introduction of a new active ingredient because of the selection of variants (bacterial or tumor cells for example) that escape the action of drug treatment. But vaccine resistance has rarely emerged. Why?
Vaccines tend to work in a prophylactic way, while drugs are therapies, *i.e.* optimal vaccines do not allow replication and consequent growth of pathogen populations. No replication no evolution. In addition, vaccines tend to induce immune responses against multiple targets on a pathogen, while drugs target very few targets. As a result, pathogen populations generate less variation for vaccine resistance than they do for drug resistance, and selection has less opportunity to act on that variation.
So far, we have been fortunate in the sense that the efficacy of most vaccines used has not been compromised by evolution. Smallpox vaccination eradicated the human smallpox virus without it attempting to evolve. The vaccine was also the best combination of antigenic stimuli, that is, the closest to natural human smallpox, which had no animal reservoirs. But neither did any strain of the measles, rubella, etc. virus emerge that could circumvent vaccine-induced immunity. The diphtheria vaccination apparently favored the more benign strain of bacteria. We do know of a few exceptions, however (8, 9).

DARWINIAN VACCINOLOGY

In 2001, the molecular ecologist Andrew Read published on *Nature* a mathematical model showing that the imperfect (very imperfect) vaccines then being tested against falciparum malaria, risked increasing the virulence of the protozoan. In the two decades that followed, the mathematical model has found several real-world applications, explaining for example the increase in virulence favored by vaccination in the case of Marek's disease of chickens, due to a herpesvirus and causing losses in the poultry industry for about 2 billion per year. The vaccine works as an anti-disease prophylaxis, and benefits the immediate health of the chickens, but it favors the evolution of more virulent strains over time and implies a run-up with gradually adjusted vaccines (there are three Marek vaccines developed so far, since 1970). Two similar cases are known in the world of animal breeding, involving some infections in farmed salmon and an avian metapneumovirus infection (7).
Mathematical models suggest that vaccines that are protective for individuals in clinical trials may nevertheless generate unintended consequences for the population. The immediate benefits of disease-fighting or imperfect vaccines mask an increased risk of evolution of more virulent strains. The acellular pertussis vaccine, compared with the earlier vaccine that contained the killed bacterium, confers shorter immunity, so there have been several recurrences of the disease, and the cause has probably been evolutionary opportunity. Acellular is preferred because it has no side effects. Several vaccine-resistant strains of hepatitis B virus have been detected and their health impact is being studied. The history of the Prevnar series of vaccines (7, 13) against pneumonia, otitis, meningitis, etc. from S. pneumonia in children and adults is an interesting case, because there are 90 distinct serotypes of the bacterium and the early vaccines intercepted 7 and 13. Prevnar 7 had reduced cases and deaths, but it had led to an evolutionary restructuring of the bacterial population, which seems to be happening with 13 as well. The restructuring is continually ongoing, and the evolution is aided by the fact that vaccination is done primarily in the United States but not in Europe and other parts of the world.
Because of microbial evolution, for human diseases such as malaria, trypanosomiasis, AIDS,

etc., vaccines are difficult or impossible to develop because pathogens use different strategies to change recognizable antigenic structures or do not show up at all by the immune system. In agricultural contexts, where immediate and economically satisfactory solutions are sought, several animal vaccines are undermined by microbial evolution. The virulence of a pathogen is directly related to replication and more pathogen also equals more disease, so every effort should be made to produce vaccines that nullify replication, and thus transmission (9, 11).

DARWIN VERSUS COVID-19

If SARS-CoV-2 were to evolve in response to an anti-COVID vaccine, it could adopt the strategy of the influenza virus, *i.e.*, continually change the surface molecules for which the antibodies work just long enough for the epitopes to remain the same. The virus would soon escape detection and it would be a matter of periodically updating, as with influenza, the anti-Covid vaccine. Evolution could lead the virus to become, under vaccine pressure, invisible and semi-innocuous, perhaps reproducing slowly or hiding in organs where immunity is less active.

A more dangerous route for us hosts would be if the virus developed a way to replicate more rapidly than the immunity generated by the vaccine. Another strategy would be for the virus to decide to target the immune system and dampen vaccine-induced immunity. As in the case of rabbit myxoma. Andrew Read and his group think that the truly evolution-proof vaccines are those that are very effective at suppressing viral replication, so they stop any further transmission.

The ideal vaccine involves: no replication, no transmission, no evolution. Furthermore, to be evolution-proof, a vaccine must activate immune responses that simultaneously attack different parts of the pathogen. It is normal for some part of the virus to mutate and evade the target, but if many sites are recognized simultaneously, immune evasion requires that many separate evasive mutations occur simultaneously. Which is highly unlikely. In laboratory SARS-CoV-2 rapidly developed resistance toward monoclonal antibodies, but struggled to develop resistance against a cocktail of antibodies, targeted toward multiple different sites. Evolution-proof vaccines protect against all circulating strains, so that no other variant can fill the void when competitors are eliminated (10).

According to Andrew Read before finding out how many have the evolution-proof characteristics, a little extra effort could be made during trials to find out if a vaccine will be evolution-proof. By running swabs on people who have received the experimental vaccine, one could determine to what extent viral levels are suppressed and by analyzing the genome of the viruses in the vaccinated people, one could check to see if an evolutionary escape is taking place. Finally, by taking blood from the vaccinated, one could calculate in the laboratory how many sites of the virus are recognized by vaccine-induced immunity.

Settling for partial or temporary relief as an effect of a vaccination strategy is unwise, because while benefits are observed for individuals, at the population level and over the long-term people remain vulnerable. And the problem is only displaced.

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