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

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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 for the past year, without most of us even realizing it. And yet, the emergence and spread in different epidemiological ecosystems of new variants of SARS-CoV-2 were self-evident facts. Facts so clear that even mathematics, usually 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 human immune responses by natural infection or by vaccine artificial training, changing their antigenic conformations. 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 the narrative 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 estimate of probability of a phenotypic variant (furin cleavage site) is sufficient to provide a sort of intelligent design. Darwin today would probably warn us about the risks of vaccination strategies that over treats (3rd and 4th doses) certain affluent populations without considering the long-term consequences at the planetary level of leaving vast part of our specie still vulnerable to the combinatorial ability of the Covid-19 virus.

Darwin and Pasteur

In the tradition of evolutionary or Darwinian medicine, Darwin is confronted with Pasteur, because the latter was, along with Claude Bernard and Robert Koch, the lord of the "proximate or immediate causes" of diseases. Such causes can be studied experimentally in the laboratory as in case of pathogenic parasites, while Darwin was 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 change in the course of descent. Pasteur's ideas and methods invented scientific medicine and generated the ambition to eliminate or control all microbial causes of disease. Except for the remote causes, those stemming from the fact that human phenotypes develop from a genomic pool selected by evolutionary adaptation by the environment, most of the accumulated "defects and predispositions" could have been arisen at the time to confer an advantage. Thousands of years

later, those same mutations, now may represent a liability in the changed environmental conditions, to the point that perhaps one day we will be asked (and able?) to correct them only with technologies more advanced than the ones of genomic editing. **In short, Pasteur allowed us to imagine and build vaccines or drugs, while Darwin explained, with his theory of natural selection, that not even with the means of the most advanced medicine we would realize the best of all possible worlds.**

Moreover, while Darwin could be defined as a layman, who followed the developments of microbiology, 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 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.

The modern concept of vaccination and its shepherd effect, is not directly related to Darwinism, because it is inscribed in an idea of immunity as a passive phenomenon and in 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 instead depends on a complex genetic-molecular architecture, which governs the dynamic, cytokines-mediated, interactions of cell populations with different roles and where the specificity of responses is then **governed** by clonal selection. An idea, that of clonal selection, that Frank Macfarlane 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 thoughts. Thucydides was 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). Likely, the phenomenon had already been reported, but the context of the "plague of Athens", where people were crowded and the disease had a rapid clinical course as being lethal or healing, facilitated its observation and description. We can also imagine that since antiquity it was realized that milder forms of a specific contagious diseases protected

from more severe forms. Alastrim, due to the variola minor species, would immunize against classical human smallpox, caused by variola major, with a mortality of about 1%, versus 30%, respectively. The widely held homeopathic magical principle that “like cures like” (*similia similibus curantur*) was probably an early intuitive interpretation for such 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 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. Precisely like any evolutionary process. After Jenner and the smallpox vaccine, which protected against human smallpox by cross immunity, the first human vaccine with live attenuated agents (against rabies) came in 1885. Both these vaccines were developed 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 pathogen, or cause adverse reactions as well as the were used without safety and efficacy controls. Back in those times, not too long ago, the political, social and health expectations and policies were very different.

Since the first typhoid vaccine in 1896, the discovery of the causative 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 1967 influenza’s 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 research and 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. In the sixties, after a series of live attenuated vaccines with 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 have 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 included those carried by viral vectors (such as the adenovirus used against SARS-CoV-2). In the same decade, conjugated polysaccharide-based vaccines (anti-H. influenzae b, anti-meningococcal C, anti-meningococcal ACW13) entered the scene. The rotavirus vaccine was the first vaccine genetically reassorted to enrich the antigen profile. Today we have the first approved nucleic acid vaccines, namely mRNA vaccines against Covid-19.

Uncertain social fortunes of vaccinations

Vaccines have improved dramatically in terms of efficacy and particularly safety as their approval process has gone through clinical trials since the 1960s. Adverse reactions are now rarer, less severe or more predictable, and incidents due to recovery of virulence from live attenuated vaccines with fatal outcomes less likely. Why is it then, if they are so much safer,

that prejudice against vaccinations is so persistent or growing? This is normal since we cannot change our perception of risk based on correct information vs. fake news alone. Human decision-making and judgment depend on or/and are controlled by heuristics biases that were acquired by natural selection to survive in EEA. In order to choose and decide, in some situations, we tend to ignore true information and prefer false ones which is 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, vaccination campaigns in Britain had to face 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 and, in part, social and political reasons that probably remain the same.

Many explanations have been given to explain the conversion/hesitancy to vaccination, some of which invoke the fact that our minds have not evolved to trust people we don't know (doctors, or – much less - an abstract entity like the State) when they tell us that there might be some minimal risk in getting vaccinated. If we do not study and understand statistics, which we were not taught by natural selection or education in the Pleistocene, we tend to 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 works 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 and communicate on the innate origin of distaste for disease and the long-lasting, sometime disfiguring and lethal effects that infections cause.

Vaccines and microbial evolution

Since spring of 2021, 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 and some of the recent variants like the Omicron seem to suggest this may be happening. But it is too early to call. One of the characteristics of Darwinian phenomena is that the variations that change the phenotype of an organism like a virus, do not arise with the *purpose* to make it "better" or optimize it, for becoming more contagious, virulent, pathogenic, etc. or all the contrary. Mutations emerge at

random, and the fact that they exhibit and preserve specific phenotypic traits depends on the replicative advantage (natural selection) in the environment where they arise. Period.

Pandemic evolution will proceed 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 foster in our societies, and not put them at risk to chase controlling a virus that is much more efficient than us in its "simple" diffusion strategies. The virus, multiplying in different ecological contexts (UK, Brazil, South Africa, India, immunodepressed 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.

Microbiologists and virologists had predicted since the beginning of this pandemic that mutations would come, even though, and it still is so, we can't exactly anticipate where on the planet they will emerge, and we don't understand precisely which portions of the genetic code of Sars-Cov-2 will be mutated. What we know is that every time a virus replicates to give rise to a copy of itself it can make an error. At the peak of the infection a human carry from 1 to 100 billion viral particles all potentially capable of generate almost as many mutated variants. In the case of coronaviruses this happens more frequently because these viral families replicate their genetic material in a "sloppier" way than humans and animals or even than some other microorganisms such as those DNA based. Coronaviruses contain single-stranded ribonucleic acid (Rna) and evolutionarily enzymes that make new copies of Rna are more prone to errors. Even though coronaviruses do not produce as many mutations as other Rna viruses, e.g. influenza viruses, because their correction enzymes repair transcriptional errors, they still produce a significant quota of mutations. For coronaviruses, it is estimated that an error occurs for every one million replicated units or, by a reasonable estimate, that each infected individual carries between 1,000 to 100,000 variants (often the same variant) to be made available for subsequent environmental selection.

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 more benign, or whether there will be a selection in favor of virulence and most importantly lethality. The first answer is easy: it depends on how the variants are changed at the level of epitopes (antigens) recognized by the immune system. This 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 based on 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 full 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 hit 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 completely compromised by evolution of the targets. Smallpox vaccination eradicated the human smallpox virus without giving it any possibility to evolve. The vaccine was also the best combination of antigenic stimuli, that is, was the closest design to natural human smallpox, which had no animal reservoirs. But neither did any strain emerge from the measles, rubella, etc. virus families 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.

Darwinian Vaccinology

In 2001, the molecular ecologist Andrew Read published in *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, that 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 of about 2 billion USD per year for the poultry industry. 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.

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, some pathogens for human diseases such as malaria, trypanosomiasis, AIDS, etc., use different strategies to change recognizable antigenic structures or do not show up at all to the immune system. These are the cases where effective vaccines are difficult or impossible to develop. 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.

Darwin versus Covid-19

If the SARS-CoV-2 virus were to evolve in response to an anti COVID vaccine, it would probably adopt the strategy of the influenza virus, *i.e.* continually mutate the surface molecules against which the antibodies work just as long as the epitopes 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 this virus would develop 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 directly dampen vaccine-induced immunity as in the case of rabbit myxoma. Andrew Read and his group believes that the truly evolution-proof vaccines are those that are very effective at fully suppressing viral replication, so they stop any further transmission.

Indeed, the ideal vaccine involves: no replication, no transmission and thus 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 the highly unlikely possibility that many separate evasive mutations occur simultaneously. In laboratory SARS-CoV-2 rapidly developed resistance toward monoclonal antibodies, but struggled to develop resistance against a cocktail of antibodies, targeted toward multiple and different sites. Evolution-proof vaccines protect against all circulating strains, so that no other variant can fill the void when competitors are eliminated.

According to Read's model 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 evolutionary 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, until the next variant or the next pandemic emerges.

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