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Commentary

Humankind versus Virus: Are we winning the battle but losing the war?

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In year 2000 the Nobel Laureate Joshua Lederberg wrote in a famous statement: "It's our wits versus their genes" [1]. The imbalance of powers in the fight against microbes is coming to light, as the Covid-19 infection is striking the world. Not by chance, Lederberg's lament concluded a recent paper with the evocative title of "Escaping Pandora's box: another novel Coronavirus" [2].

Yet, are we entitled to use the whole of our minds, and therefore the technological knowhow and the economic resources to tamper with an epidemiological climax?

These approaches appear reasonable, but they have prompted in recent years cyclical phases of panic and of unjustified fear, that strongly impacted on the economic and on the social systems. This led to a reactive rather than a proactive strategy piloting the resources towards the research of tailored measures aimed to produce acute responses to the crises. Nevertheless, this approach resulted, in the best case, in the production of vaccines and antiviral drugs whose use – although extremely welcome – may be effective only when an epidemic is already in place. Besides, these and standard public health measures commonly put into place in the case of an outbreak have not so far produced permanent solutions, aside from a few cases (e.g. SARS-CoV-2).

During the onset of an outbreak and of a subsequent epidemic, some studies are essential to define the picture and the possible solutions. Among those: the syndromic surveillance associated with targeted viral testing, household studies for detection of risk factors and infection timing, community studies, the ability of integrating data from different sources, viral shedding studies and obviously case controlled trials [3]. However, these strategies cover only partially the whole of the issue. Only a few models are commonly used to better understand how the enemy, namely the virus, and how we – intended as the target of the virus – work. Does concentrating our best efforts and resources during the acute phase of the disease really equal to using the best of our wits against the best of their genes? Is this a lose-to-lose situation, considering how fast a virus can evolve (up to 1% of that genome per day [2])? We can speculate that the target may be the development of broadly protective vaccines, able to cover a whole class of viruses. This is the case of influenza [4], even if the goal is still far from reach.

The main point, however, is that what we still do not know is disproportionately vast compared to what we know. Viruses can evolve faster than our knowledge grows through research. Whereas the complexity of the

human being is an opportunity for a reasonably simple lifeform, this same complexity represents a major hazard in understanding how the countless variables of our organisms interact with the virus.

To name a few of the factors involved, we can reason that although thousands of studies show the relation between food and immune response [5], and thousands show the relation between immune response and resistance to viral infections [6], there are basically no reliable studies on the subtle interaction of those factors: nutrition, immunity and viral infection.

We can classify the relationship among nutrition, immune response and individual antiviral defences according to different criteria. From a clinical point of view, we highlight some of the main issues to which research must provide answers:

a. Are there dietary regimes or specific active ingredients (such as micronutrients present in functional food) capable of boosting the immune system in the acute phase? Or, vice versa, are nutritional deficiencies (secondary to poor diet habits or to specific medical conditions) that may increase the probability of getting an infection, as well as the gravity and the lethality of such infection?
b. Can food and the way people eat facilitate the circulation of the viral infection? Can food pollution facilitate the development of viral disease as air pollution does?
c. Besides the acute phase of an epidemic, are there diets that can protect from viral infection or, on the contrary, are there foods or diets that can augment the risk of transmission?
d. Are there some connections between the human microbiota and the selection processes of pathogenic viruses or with the sensitivity/resistance mechanisms?

A flourishing but highly unreliable literature has covered most of the issues related to point a) and broadly to the strengthening of the immune system. Different foods and diets have been allegedly tested, but there is no evidence so far that the claims on the effects of these single nutrients on the immune system are trustworthy. Therefore, physicians should be aware that the declared protective effects probably depend on a placebo effect, and prescriptions should be based on an ethical basis.

In fact, the syllogism "a given substance *A* can have an effect on the immune system" and "the immune system defends from infectious diseases" therefore "I can cure a patient with A" do not have scientific foundations, although an hypothesis could be considered whose outcome should be tested according to a shared systematic method. We therefore encourage research in this field based on rigid scientific criteria [3].

On the other hand, it is known that severe malnutrition (also intended as overnutrition or severe deficit of one or more nutrients) can facilitate, in a nonspecific way, infections, Covid-19 included. Those medical conditions have to be considered as a particular class of comorbidities. Those come together with the ones that typically affect elderly people. Nevertheless, younger people are not immune: this is known for those who have an unbalanced diet, but more specifically for those affected by eating disorders.

Although of high interest, this is a relatively unknown field. This is to do with the intrinsic complexity of those clinical cases where more then one disease affect a patient. Thus, malnutrition – here considered as a medical condition - has to be properly addressed, even when specific evidence is missing, on the basis of ethical considerations and of pathophysiological reasoning. There are in fact a number of clues that point of the link between nutrition, low grade inflammation and susceptibility to viral infections. Since the first studies by Beck on the deficit of selenium in relation to the virulence of the *Coxsackie* virus [7], it was suspected that the complex relationships between nutritional status, virome [8] and microbiome [8–10] are also fundamental in determining resistance to infections and probably also in the selective processes of new viral strains, with or without the involvement of animal reservoirs.

The symbiotic system among virus, bacteria, cells and organism is of the highest complexity. Moreover, there are not enough studies to start to understand the net of connections among different observed phenomena and the single and multiple relations among them, as per the systems medicine approach. Yet, some interesting data arrive from studies evaluating the diet in children suffering from upper respiratory tract infections [9] or from some relevant population studies of the last century.

We still do not know why Pandora's Box is now open and why viruses and particularly coronaviruses (in less than two decades, three new streams with a high rate of transmission and mortality originating from animal reservoirs: Covid-19, SARS-CoV, MERS-CoV) [11] started to come out of the box. Although we may speculate that different causes may explain what is happening today – ranging from different scenarios such as climate change, dietary and lifestyle changes, population growth, and so on – there is still no evidence, but only hypotheses that we can work on.

This remains a key issue, indeed. We have to study the problems in depth, to methodologically and systematically measure what we observe, keeping an open mind. We cannot research these issues only in the case of a clear and present danger and only when a new emergency arises, tackling only single problems to find patch-like solutions. On the contrary, we have to focus on the human health as a whole, starting from nutrition and the proactive management of the environment we live in.

We have in fact to open new pathways and new fields of research, as suggested by some recent studies on common virus receptors and human lipoproteins [12, 13], or the newest ones showing how omega – 3 and -6 fatty acids suppress MERS-CoV and other coronavirus replications [14].

In conclusion, we call for new approaches, guided by the brave intent to address them, starting from new and suggestive visions that potentially have an enormous impact on what we know about what we are and the world we live in.

Disclaimer

The information in this article is intended for medical professionals, researchers and experts in this field. This is not a practical guide for the Covid-19 infection. Public health authorities and physicians are the primary source of information for the prevention and the management of the infection.

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