Call for a UN International Agency to regulate and control research on pathogens with pandemic potential

It is our collective responsibility to ensure that technology is applied for the common good. To cite the most celebrated case, research in nuclear physics led to the discovery of nuclear fission and the development of nuclear reactors, but also nuclear weapons. Nuclear technology is burdened with deep and obvious moral and ethical issues that led the United Nations (UN) to create the International Atomic Energy Agency.

The hugely disruptive COVID-19 pandemic should trigger an analogous response to address the risks inherent to research on enhanced pathogens with pandemic potential (ePPP).

We propose the creation by the UN of an International Pandemic Pathogen Agency (IPPA) defined as the world's central intergovernmental forum for scientific and societal cooperation in the ePPP Framework. IPPA will work for safe, secure and peaceful uses of ePPP Research, contributing to international health, safety and security, and the UN Sustainable Development Goals.

There are arguably enough "International Agencies". Why do we need yet another one? Let us briefly present context and arguments for the creation of IPPA.

Like other biomedical sciences and technologies, virology has made phenomenal progress in recent decades. This raises disturbing ethical questions, particularly about the creation of novel viruses or manipulation of existing ones. We are extremely concerned about some virological research activities that are referred to by specialists under three names, namely "Gain of Function Research of Concern" (GOFROC), "Dual Use Research of Concern" (DURC), and research on "enhanced Potential Pandemic Pathogens" (ePPP). Those definitions lead to endless discussions, which we propose to set aside by selecting the term ePPP, which seems increasingly favored, particularly in the USA.

ePPP research seeks to understand the mechanisms whereby viruses pass from one species to another, adapt in terms of transmissibility and lethality, and react with the host's immune system. It seeks to identify, classify and characterize all viruses present in the biosphere, to predict which ones are the most likely to infect humans and generate pandemics. Those are legitimate questions, whose ultimate goal is to predict and prevent the transfer of viruses from wildlife to humans, that is to say zoonoses. ePPP research is promoted within the One Health concept, in which humans are considered as a component of the biosphere, the global network of all species and microorganisms, and their environment. The One Health concept makes sense. It is easy to explain, easy to understand and easy to sell to media. However, what is rarely if ever discussed is that, like all research, ePPP work is not exempt of difficulties and potential deleterious consequences.

A typical ePPP project begins with collecting samples containing potential viruses from wildlife, mostly mammals and birds, sometimes other vertebrates and even invertebrates, more rarely microorganisms (fungi, bacteria…). In principle, sampling is performed by specifically trained

personnel, in appropriate conditions of personal protection and animal handling. Plasma and other body fluids are processed or frozen for analysis in laboratories. Among the most important analyses are DNA/RNA extraction and sequencing, and virus isolation, identification and study by inoculation of different types of cells in culture.

Samples are studied in laboratories with four increasing levels of BioSafety Levels 1 to 4 (BSL-1-4), also named Pathogen levels 1-4 (P1-P4). For example, processing for DNA/RNA extraction inactivates viruses, and samples can then be studied at BSL-2 (sometimes even BSL-1) level, which is standard. Samples potentially containing active pathogens such as SARS-CoV-2, are studied in BSL-3/P3 conditions. When highly pathogenic viruses such as filoviruses (Ebola, Marburg) are suspected, work is carried out in a BSL-4/P4 laboratory. As we write (autumn 2022), there are an estimated number of sixty to seventy P4 laboratories in the world. Some are not reported or in construction, but it is reasonable to assume that they number less than one hundred. The precise number of BSL-3 laboratories is unknown, but estimates are about 1500 worldwide, and they probably do not exceed twice that number. In parallel, there is a need for highly qualified personnel to operate those laboratories, an issue that is often overlooked. Be that as it may, if ePPP programs are carried out as planned, many more P3 and P4 laboratories and competent personnel will be required to carry out the required experiments. Past experience showed that accidents do occur even in the best operated facilities. For example, the SARS-CoV virus, which caused the SARS epidemics in China in 2002-2003, later leaked at least 4 times, leading to some human loss but, happily, limited local spreading. A leak of SARS-CoV-2 was well documented in a Taiwan laboratory. Recent revelations and publications show that highly risky ePPP experiments are being carried out right now, in P3 and P4 laboratories all over the world, some of which are located close to densely populated centers. The risk of accidental release associated with each individual experiment is low and will decrease with improved facilities, better operational practice and experience. But the global risk will increase considerably with the proliferation of experiments and facilities.

Another issue, recently outlined by a group of US experts, concerns the risk of a pandemic to society and economy, and not solely health. An unanticipated feature of COVID-19 is that a virus like SARS-CoV-2, which is not overly aggressive with a lethality (Infection Fatality Rate, IFR) around 1%, but high transmissible, can disturb hugely the workings of our modern society. During lockdown, COVID-19 brought our society almost to a halt. Let us imagine what the situation would have been had the lethality been only threefold higher. Food and the most basic supplies would have become scarce, solidarity would have reached its limits, and dramatic societal troubles would have ensued. Our modern civilization is extremely fragile. In addition to the health issues and related problems (medical personnel, hospital beds and medical supplies), it is imperative to factor in the equation the risks to society and economy. One way to approximate this is to estimate the risk of a pandemic virus not simply in terms of its danger to human life, but also in terms of its transmissibility. A relatively mild virus can become a high risk when it is highly transmissible, as occurred with SARS-CoV-2. This is key to prevention and handling of future pandemic, and therefore to any evaluation of ePPP research projects and programs.

Last but not least, modern means of international transport have contributed to the ultrafast spreading of SARS-CoV-2. Any incident that occurs at any given location on Earth poses an almost immediate risk all over the world. Prediction and prevention are an international, not solely a national affair.

So, what can be done?

Attempts to regulate risky ePPP experiments were initiated in the USA in 2012 following controversial experiments with bird flu viruses carried out in the United States and in the Netherlands. A statement by the "Cambridge Working Group" of scientists, argued against such research (http://www.cambridgeworkinggroup.org/), whereas another group supported it (http://www.scientistsforscience.org/). Discussions with the Obama Administration led to a moratorium in 2014, which was applied laxly by NIH, NIAID and other grant agencies, to be finally lifted in 2017. The moratorium was replaced with the elaborate "Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens", abbreviated as P3CO (Potential Pandemic Pathogens Care and Oversight) (https://www.phe.gov/s3/dualuse/Pages/p3co.aspx). P3CO procedures have not been implemented too zealously and are mandatory only in agencies that depend on the Human Health Service Department, such as the NIH, but not the Department of Defense or private NGOs. Nevertheless, it is worth emphasizing that the P3CO framework is extremely useful and can serve as model for future action. Other countries proved less prone to control ePPP research than the USA. Intriguingly, apart from isolated attempts and alerts, there is almost zero debate on risks and control of ePPP programs: Rare discussion in the USA, and less still in the EU, UK, Japan, China, India and other countries, even those with a sound scientific tradition.

To draw a parallel with the past, public protest about nuclear arms was widespread. To draw a parallel with the present, protest against climate change has long been accepted. Thanks to many discussions about COVID-19, even citizens with a limited scientific background now understand enough to realize that there is indeed something to worry about. And yet ePPP research remains under the control of direct stakeholders, with unavoidable conflict of interest. Although professional scientists (virologists, epidemiologists, public health experts) are key stakeholders, the debate must not be left solely in their hands because the question concerns everyone. To paraphrase Georges Clémenceau "Regulation of ePPP work is too serious a matter to be left to virologists alone." The general public and politicians must take a more active part.

A future IPPA must have international coverage, with authority to inspect, monitor and regulate activities in virology and epidemiology laboratories in each member country. The aim is not to slow the pace of biomedical disciplines or restrict academic freedom, but to foster a win-win situation. IPPA is not meant to interfere with activities in each individual country, which is best left to local governments and institutions, but to set guidelines with force of law, to make sure laws and rules are followed, to report problems and ultimately recommend sanctions if need be. IPPA must be under UN jurisdiction to act with justice for all member countries. Ideally, it should avoid redundant bureaucracy. The WHO might be well suited to regulate ePPP, as proposed by the

Lancet COVID-19 Commission (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01585-9/fulltext). However, WHO lost credit by yielding to political pressure while handling the COVID-19 pandemic. To restore confidence and regulate ePPP, huge reforms and a revised charter would be needed. A new UN Agency is preferable.

Until IPPA is operational, a temporary moratorium should be implemented with as great an international reach as possible, while responsible nations review the experimental alternatives, possible risk mitigation measures and risk/benefit evaluation criteria.

The next pandemic is right about the corner! Let's keep it there. Let's urgently request a moratorium and the creation of IPPA to control and regulate ePPP research. It is a matter of life and death.

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