An Overview of Biological Warfare and SARS-CoV-2 as a Potential Biological Agent

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Abstract

The conflict between humans did not stop throughout the ages, and humans have used everything in nature to serve this conflict since the first ages of history, during the First World War when the world witnessed the actual use of chemical weapons, and nuclear weapons during World War II By the United States of America against Japan, which greatly developed a biological warfare program before and during World War II, and a lot of information regarding this program was withheld by an agreement between Japan and the USA after Japan's defeat in the war. Finally, the countries of the world succeeded in signing a Biological Warfare Convention (BWC) in 1972, and the Ninth Review Conference will be held for this convention during 2021 to discuss its articles and try to develop its mechanisms to prevent the development and use of biological weapons in the conflict between nations.

According to the British novelist George Orwell, "Life is a race between education and catastrophe". As the great development in the field of genetic technologies and the production of vaccines collided with the emergence of new pathogens, the latest of which is the emerging SARS-CoV-2 virus that caused the COVID-19 pandemic around the world, and once again the major countries have been accused by each other of spreading this virus in the world intentionally or by accident. We must carefully examine these allegations before making decisions, because these allegations may have negative repercussions on the future of humanity.

Key words: biological, warfare, weapons, BWC, genetic engineering, COVID-19 pandemic

Introduction

Biological weapons intentionally use pathogens to cause death or harm to humans, animals or plants. Modern biological weapons (BW) and nuclear weapons belong to the category of weapons of mass destruction [1]. Infectious diseases have been used as weapons during conflicts throughout history, and the availability of a number of criteria makes infectious diseases more powerful and ripe for use in biological warfare or bioterrorism, which include:
1) High morbidity and lethality.
2) Severe infection or high toxicity.
3) Mass production and storage without losing the possibility of causing diseases.
4) The possibility of being widespread and with little resistance to delivery operations.
5) Resistance to environmental factors after spread, causing injury and disease.
6) Be suitable as a biological agent in terms of the potential for developing the genetic engineering and weaponization process [2].

The National Institute for Infectious Diseases and Allergy in America (NIAID) has classified pathogens within a list of pathogens likely to be used the most in biological warfare, and that represent a threat to national security and public health andit divides into three categories (A, B and C). This classification depends on the ease of separation and transmission, mortality rate, public health readiness and degree of public panic and chaos in society.

Richard Preston's novel "The Cobra Event" published in 1997 was fictional, including the bioterrorism scenario with the deployment of genetically modified superviruses. Preston says: "To think that the power of the genetic code is not being bent toward weapons is to ignore the growing body of evidence, the lessons of history, and the reality of human nature. As Thucydides pointed out, hope is an expensive commodity. It makes better sense to be prepared." [3], US President Bill Clinton's reading of this novel raised his concerns about the threat of bioterrorism and bioweapons, so he issued two presidential directives to address the deficiencies in national security related to bioterrorism and biological and chemical warfare [4].

Human coronaviruses were not considered harmful before the year 2002, and they were a common cause of influenza, and unlike animals, coronaviruses did not cause serious diseases to humans, but that has changed completely since 2002, when three new dangerous human coronaviruses appeared: SARS-CoV, MERS-CoV, and SARS-CoV-2 (the cause of COVID-19) [5]. In the mechanism of viral infection there are two proteins involved in viral penetration of cells, Angiotensin-Converting Enzyme II (ACE2) and Trans-membrane protease, serine 2 (TMPRSS2) [6]. Coronaviruses have a special host, and depending on the spike protein that its special shape fits only one host, and the shape of this protein is determined by the S gene, so if the coronavirus jumps to a new host, this leads to change in the S gene, which is not caused by a small group of point mutations. A significant change in the S gene was found in the three coronaviruses, therefore there are two possible reasons for this big change: recombination which is a natural process or genetic engineering [5].

History of Biological Warfare and Biological Weapons program in the World

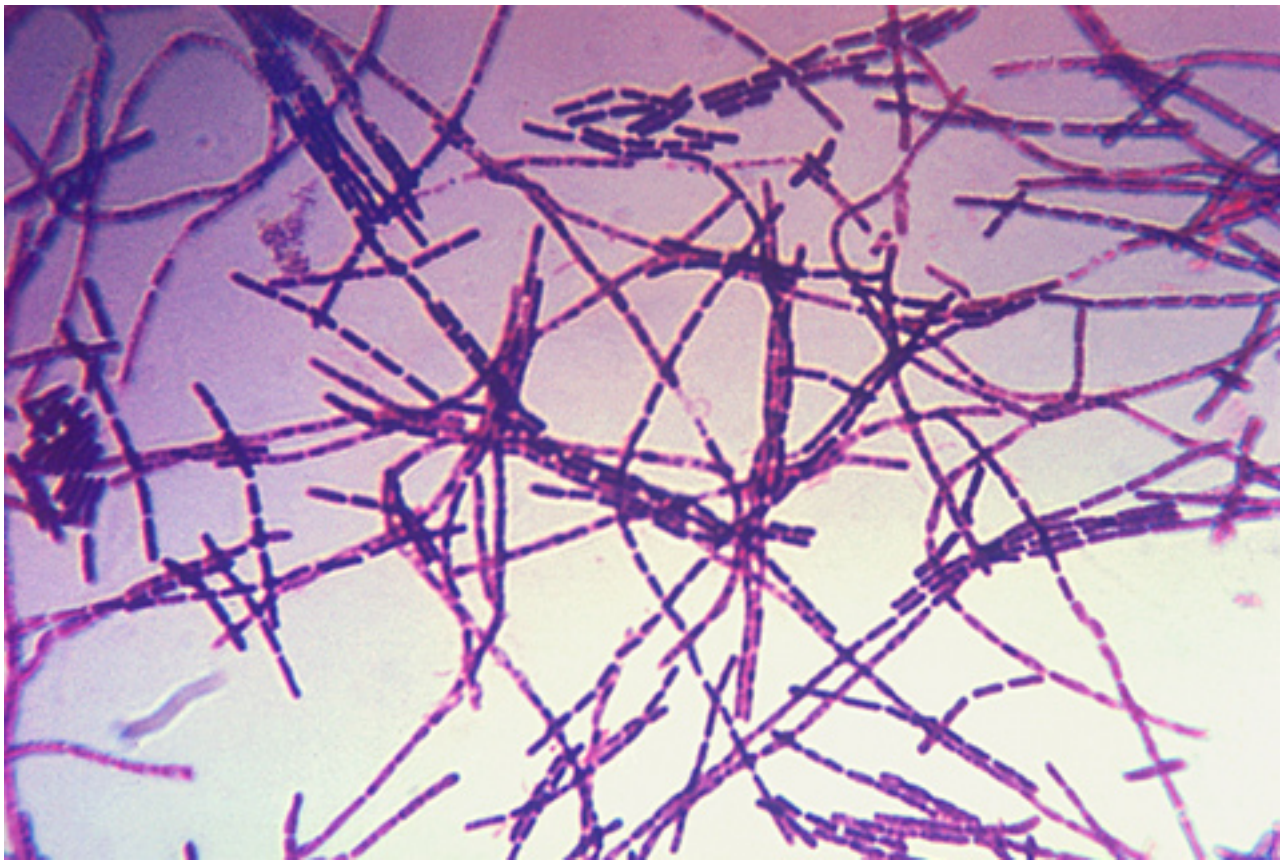
Attempts to use biological weapons began in 148 BC when Hannibal ordered his soldiers to bring pottery vessels that he filled with poisonous snakes and threw them on the back of enemy ships, it was also reported that in ancient civilizations such as the Greeks, Romans and Persians, warriors polluted the drinking water of hostile parties, either with the corpses of dead animals or decomposing human corpses. In 1346 AD the Tartar army retained victims of the plague disease in the city of Kaffa (Feodosia, Ukraine) until the infection passed to uninfected people in this city and they were exterminated, and in 1763 AD the British army provided assistance to Indians in the form of blankets that were used by plague patients [7].

Biological warfare as we understand it today is a modern concept that did not exist until the middle of 19th century as a result of the research of both Pasteur in France and Robert Koch in Germany, which showed that microorganisms cause diseases. Before that it was believed that disease occurs for supernatural reasons. Therefore, it is not surprising that the Romans used the same word *veneficium* to denote poisoning and practicing sorcery[8].

The beginning of modern microbiology came with Casimir-Joseph's success in isolating anthrax in 1863, and Robert Koch's success in obtaining pure culture of *Bacillus Anthraces* (Figure 1). Koch's hypotheses [9] allowed him and other scientists to isolate, produce and store of specific microorganisms, which had a great impact on potential biological warfare. Concerns were noted at the international level in Brussels in 1874 when the International declaration on laws and customs during War included a ban on poisons and poisoned arms [10].

Fundamental evidence indicated the existence of an ambitious biological warfare program in Germany during World War I, and numerous allegations were made that it was characterized by covert operations. During World War I numerous reports circulated that the Germans attempted to ship horses and livestock inoculated with pathogenic germs such as *Bacillus antracis* (the cause of anthrax), and *Pseudomonas pseudomallei* (that causes glanders) to USA and other countries, as well as the use of the same aforementioned pathogen to transmit the infection to Roman sheep that were intended for export to Russia, as well as other allegations of German attempts to spread cholera in Italy and the plague in Saint Petersburg in Russia. The Provisional Subcommittee of the League of Nations, which was formed of multiple nationalities in 1924, confirmed that there is no conclusive evidence of the use of biological weapons during this war, but the document issued by this committee confirmed the use of

Figure (1): Micrograph of Gram-positive anthrax bacilli [11]



chemical weapons by German forces [12]. in comparison with Americans who had barely developed ricin, a toxin extracted from castor beans by 1918, and was not yet ready for use in war [13].

All this prompted global diplomacy to work to limit the proliferation and use of biological and chemical weapons. On June 17, 1925, the Geneva Protocol was signed by 28 countries. This document did not address issues related to verification and compliance with the commitment to it, which made it "toothless" [10].

During World War II, many countries began ambitious research programs of biological warfare. Allegations and counter-allegations loomed over events during and after World War II [12]. Many studies indicate that about 20 countries developed biological weapons programs between the years 1945 and 2015, which differed in their size and sophistication. The largest biological weapons program was in the Soviet Union (about 60,000 scientists, engineers, technicians, and others were employed), while the smallest one was in Rhodesia (currently Zimbabwe), where the number of workers did not exceed about six technicians. It's known that only the USA and the Soviet Union developed operational capabilities to spread biological agents over large areas using sophisticated aircraft and missile launch systems. Many programs were terminated before the final negotiations on Biological Weapons Convention (Canada, France, United Kingdom and USA), In some countries (France and United Kingdom) a competition occurred between biological weapons and nuclear weapons, and nuclear weapons were given priority and allocated resources because they were considered more strategically important [8].

Japan conducted a research program related to biological weapons from 1932 until the end of World War II. The program was under the supervision of Shiro Ishii (1932-1942) and Kitano Misage (1942-1945). Many units of the Japanese army were established related to research and development of biological weapons, the most important of these was "Unit 731", which was stationed in Manchuria near the town of Benevgan, as Shiro Ishii gave permission to build the first major facility in the world related to biological warfare in this town in 1932. The annual operating cost was estimated between 6-12 million yen [10]. The most important pathogens involved in this program were: *B. anthracis, Neisseria meningitides, Vibrio cholera, Shigella spp* and *Yersinia pestis*. In subsequent years Japanese officials considered these experiments "unfortunate" from a human point of view [12].

The United States' biological weapons program began in 1942, and included a research and development facility at Camp Detrick in Maryland (renamed Fort Detrick in 1956, and today known as the United States Army Medical Research Institute for Infectious Diseases [USAMRIID]), and with test sites in Mississippi, Utah, and a production facility in Terra Hot, Indiana. The microorganisms that the program looked at were *B. anthracis* and *Brucellasuis.* Despite the production of about 5,000 bombs laden with anthrax bacilli at Camp Detrick, the production facility lacked engineering safety measures which prevented the production of these biological weapons during the Second World War on a large scale [12]. The United States ended the American bioweapon program in the year 1969 by US President Richard Nixon (the work on poisons did not stop until later), as the US National Security Agency confirmed

the lack of strategic viability of biological weapons, and they came to the conclusion that these weapons did little to the security of the USA, as it complicated Arms Control Negotiations with the Soviet Union [8].

At the same time, the Soviet Union doubled its efforts in the field of offensive and defensive biological research. Numerous reports were mentioned in the sixties and seventies of the twentieth century despite the Soviet Union's official claim that it did not possess any biological or chemical weapons [12], and in 1989 the Soviet scientist Dr. Vladimir Pasechnik (responsible for the former in the Russian biological weapons program Biopreparat) revealed that the Soviet Union maintained a stockpile of 20 tons of smallpox virus that was cultivated in eggs, and was constantly replenished when the previous stock lost its validity, and he also claimed that the Soviet Union built three factories in wartime with an estimated production capacity of 1,800 Tons of Bacillus anthracis. Pasechnik's allegations centered on four points related to the Soviet Union's biological weapons program: (1) the Soviets possessing genetically modified bacteria and viruses, (2) they prepared weapons from them in the form of powders, (3) they loaded them in various munitions, (4) they introduced biological weapons into their combat doctrine and set specific plans for the use of those weapons [4]. It is not clear if the Russians ended all activities of the former Soviet biological weapons program. In 1992, former Russian President Boris Yeltsin admitted that the Soviet Union had operated programs to develop biological weapons in contravention of the obligations of the BWC and promised to end it, and the Russian government officially recognized some of its previous activities in a report to the United Nations in 1992, but it retreated from this recognition by the year 1994 [8].

Biological Weapons Convention

Global efforts to limit the proliferation of biological weapons began after the First World War, and the Geneva Protocol of 1925 (the Protocol for the Prohibition of the Military Use of asphyxiating, poisonous or other gases, and of all analogous liquids, materials or devices and bacteriological methods of warfare), which banned the use of chemical weapons as well as biological weapons. In the 1930s, many attempts were made to prohibit the production and storage of Biological weapons at the World Conference on Disarmament, but the attempts were unsuccessful due to the conference's collapse in 1937 [1].

On April 10, 1972, the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and the destruction of those weapons was signed, also known as the Biological Weapons Convention (BWC) [14], which prohibited the development, production, storage or possession of biological agents and toxins. This agreement was opened for signature in London, Moscow and Washington on April 10, 1972, and it entered into force on March 26, 1975 after 22 governments deposited ratification documents, including the depositary governments, and this agreement is valid for an unlimited period and requires if withdrawing from it, giving advance notice of three months. The number of state parties to this convention reached 183, and the number of signatory states 109. We point out that Israel is still not a party to this convention and has not signed it yet (it participates in the review conferences of this convention as an observer). Under this convention, the states parties undertook to submit annual reports, using agreed forms, on specific activities related to the BWC including: data on research centers and laboratories; information about vaccine production facilities; information on national biodefense research and development programs; publicize past activities in offensive and/or defensive biological research and development programs; and information on the spread of infectious diseases and similar events caused by toxins; disseminating results and encouraging the use of knowledge and communication; and information on legislation, regulations and other measures, and the agreement stipulated that a "review conference" be held five years after its entry into force to review its operations, where the Preparatory Committee for the ninth Review Conference was postponed due to the COVID-19 pandemic as agreed at the Meeting of States Parties, the Preparatory Committee held at the Palais des Nation on 20 December 2021. It resumes its work in April 2022 (United Nations, 2022).

Biological Weapons and Genetic Engineering

Genetic engineering techniques began in the seventies of the last century, and in the eighties it became a global industry generating billions of dollars in profits, which increased exponentially during the last decade of the twentieth century [4]. In 2007; Garfinkel et al. estimated the number of companies that manufacture DNA in all parts of the world that are capable of providing gene and genomic products to about 45 companies (24 of which are in the United States alone and the rest are distributed in the rest of the world) [15]. In 2009 the International Gene Synthesis Consortium (IGSC) was established, which is a commercial industrial organization that aims to promote the beneficial application of technologies synthesizing genes while preserving biosecurity [16], and the Union also works to this end with governmental and international organizations and other interested parties to achieve this goal. IGSC members account for approximately 80% of gene manufacturing capacity around the world (IGSC, 2021).

Genetic engineering did not have a major role in the early stages of biological warfare, as some pathogens found in nature (such as smallpox, plague, anthrax) are dangerous and deadly enough in themselves, and genetic engineering was not necessary for these agents to be used as biological weapons. Some studies indicated that the former Soviet Union had reached, through a biological weapons program, the so-called "Invisible Anthrax", which resulted from the introduction of a new gene into *anthrax bacilli,* which changed its immune characteristics, and made it resistant to existing conventional vaccines, which turned out to be ineffective against this new, genetically modified strain [17].

The development of effective biological weapons relying on genetic engineering requires an extensive research program with adequate resources, which may encounter several obstacles that must be addressed, namely:

- Buying strains of appropriate agents.
- Mass production of agents without loss of pathogenicity.
- Development.
- An effective means of delivery.

The third step in particular is very difficult and rarely accomplished, and we can say that, with the exception of the previous massive biological warfare programs in both the United States of America and the Soviet Union, after years of the active programs, only initial methods have been developed for the delivery of these biological agents. Accordingly, genetic engineering is a relatively late step in developing biological warfare capabilities, which will not be used until the basic first steps are completed. We must not lose sight of the fact that some natural pathogens are not suitable for use as biological agents in the military field, which would happen when the following requirements are met:

- Mass production.
- The speed of the effect.
- Resistance to environmental factors.
- The possibility of treating the disease caused by these agents, or the availability of an appropriate vaccine, which allows the protection of individuals (soldiers) who use such weapons.

Anthrax is the first choice here, since the pathogen (*anthrax bacillus*) meets nearly all of these requirements. Potential victims of an anthrax attack can be treated with antibiotics even several days after infection, as evidenced by the 2001 anthrax attacks in the USA [17].

Tight restrictions are imposed at the present time on access to dangerous pathogens, in particular Smallpox, which was eradicated in 1980 (WHO, 2021) and it is preserved and stored officially only in laboratories with high security measures in each of the United States of America (Center for Disease Control and Prevention "CDC" in Atlanta) and the Russian Federation (the Russian Center for Virology and Biotechnology "Vector" in Koltsovo) [18]. Ken Alibek published in his book "Biohazard" that the former Soviet Union was conducting research related to the introduction of genetic modifications to the smallpox virus in 1992, in addition to that by 1992; the Soviet Union had produced 52 different pathogens or a combination of these agents, including the deadly Marburg virus, Ebola virus and smallpox virus, which had been placed within weapons suitable for use. The agents, including the most infectious and easiest to produce and transmit microbes, were labeled "battle stains", and the "836" anthrax was the best among the battle strains, according to Alibek [19].

The success of the experiment of a research team at Stony Brook University in New York to synthesise the polio virus (not considered a biological weapon) starting from scratch, as they built small sequences of DNA and merged them together to form the complete genome of this virus (which is available on the network), then this synthetic virus was activated by adding a chemical mixture, which made it an active and pathogenic virus [20]. This experiment sheds light on the great development that molecular biology has reached and sheds light on its problems as well. In principle, it is possible to use this technology to synthesise other viruses with a short DNA sequence. This includes at least five viruses that are considered potential biological agents, including: Ebola virus, Marburg virus and Venezuelan equine encephalitis virus. As for Smallpox, the assessment of the current risks related to it, and although it is considered a very effective and ideal biological weapon, the possibility of using it for biological attacks is very low, as countries other than the USA and Russia can't access it, but if it becomes possible to reconstruct the genome of this virus in laboratories (DNA sequence of the virus genome is available on the world wide web), this assessment will change, and the relative safety that we assume today will disappear. We note here that the poliovirus synthesis technology can't be applied in the case of smallpox virus (the virus genome is very large), even if the complete genome sequence of the virus can be reconstructed in the laboratory, converting it into an active and effective virus is very difficult, but there may be other methods for this, including starting with a closely related virus such as monkey pox or rat pox virus, and then changing the bases and DNA sequence to reach the human smallpox virus [17].

The viral genome synthesis technique has become possible thanks to advances in many fields of science, including the use of restriction enzymes to genome synthesis and sequencing techniques, such as the 454 Roche, Illumina, and SOLiD systems. The synthesis of the synthetic genome was performed by a combination of two different strategies: chemical synthesis and PCR amplification [21]. PCR technology is widely used in the field of biology, which uses the enzyme DNA polymerase [22]. Although treating viral genomes with the aim of modifying viral properties has become routine in many laboratories, developing completely new artificial genomes without using templates and genetic circuits as units to assemble genomes is a new topic and remains relatively ambiguous and involves security risks that must be answered before this method becomes popular. The creation of completely new viral genomes is one of the most promising techniques for developing new, more effective and selective antibiotics, as well as for preparing vaccines and antiviral drugs with fewer side effects, as well as in the detection of living microorganisms in hospitals and manufacturing places where strict control of these microorganisms is essential [21].

A research group from the University of Bern has published a paper entitled "Rapid Reconstruction of SARS-CoV-2 Using a Synthetic Genomics Platform" in which the authors say they are able to engineer and activate chemical-synthesized clones of the emerging SARS-CoV-2 virus through a yeast-based synthetic genomics platform

template, where they formed parts of the viral genome using viral isolates, cloned viral DNA, clinical samples, or synthetic DNA, and then these parts were reassembled in one-step in yeast template "*Saccharomyces cerevisiae*" using transformation-associated recombination cloning to maintain the genome as a yeast artificial chromosome. Then the researchers in this study used the enzyme T7 RNA Polymerase to activate the virus, and that was only one week after obtaining the DNA fragments [23]. Scientists resort to these technologies with the aim of accelerating access to treatment and development of vaccines, but due to the dual-use nature of this technology (it has high biosecurity risks), care must be taken regarding publishing the results of such research without observing biosecurity/ safety rules [24].

The mutation rate is defined as the probability that the change in the genetic information will be transmitted to the next generation, and in viruses the generation is often defined as a cell infection cycle, which includes (attachment to the cell surface, entry, gene expression, replication, encapsulation and release of infectious particles). Mutations are not limited to replication because they may also result from modification of the genetic material or spontaneous destruction of DNA. The mutation rate should not be confused with the frequency of mutations for a particular viral group. This frequency is a measure of the genetic variation, which depends on the number of processes such as natural selection, random genetic drift, and recombination. High mutation rates lead to greater genetic diversity, but we cannot directly infer the mutation rate from the frequency of the recorded mutations of a viral group [25], and knowing the rate at which virus mutation occurs is important to understanding their evolution and mechanisms of combating them, as the results of a study to estimate the rate of mutation occurrence using a new statistical method conducted by Rafael Sanjua'n and colleagues in 2010 indicated that there is a negative correlation between the rate of mutation and the size of the genome in both DNA and RNA viruses [26], and it can be said that the rate of viral mutations ranges approximately in a range between 10-8 – 10-4 per nucleotide per cell infection, in DNA viruses; this range was 10-8 – 10-6 (s/ n/c), while in RNA viruses it ranged between 10-6 – 10-4 (s/n/c). These differences have many mechanisms, one of them that the vast majority of RNA viruses lack the 3'-exonuclease needed to correct the error, therefore it is more error-prone than DNA viruses, and the exception is Corona viruses, which are Positive-strand RNA viruses that contain the RNA polymerase in which the 3'-nuclease, Unlike all other known RNA viruses, it has developed an error-correcting ability, and it also has the largest genome among RNA viruses (30 - 33 kb) [25].

Is SARS -CoV-2 virus a Biological agent?

First, we must ask the question about the impact of the Corona pandemic on the state of the global economy, which is greatly affected by the economic situation of China (the second largest economic power in the world), and the question is about the beneficiary of a contraction in the Chinese economy, as several economic reports indicated that the rate the overall GDP growth in 2020 was as follows:

- The United States of America ranked first with 22.3 trillion US dollars.
- Then China with 15.7 trillion US dollars (but at a higher rate of growth than the United States of America).
- Japan, third, with 5.4 trillion US dollars [27].

The world's great powers accuse each other of being behind the spread of the new Corona virus, as Americans refer to the participation of Chinese facilities in this process (Wuhan Institute of Virology, Wuhan, the center of the virus's spread at the beginning), and in return China accuses the United States of America of having military laboratories to produce biological agents around the world, and the Israelis blame the Chinese, while the Russians blame the Americans, but there has not yet been any scientific evidence for these allegations, which can be compared to the period after World War II when the conflicting powers resorted to accusing each other of using biological weapons [28].

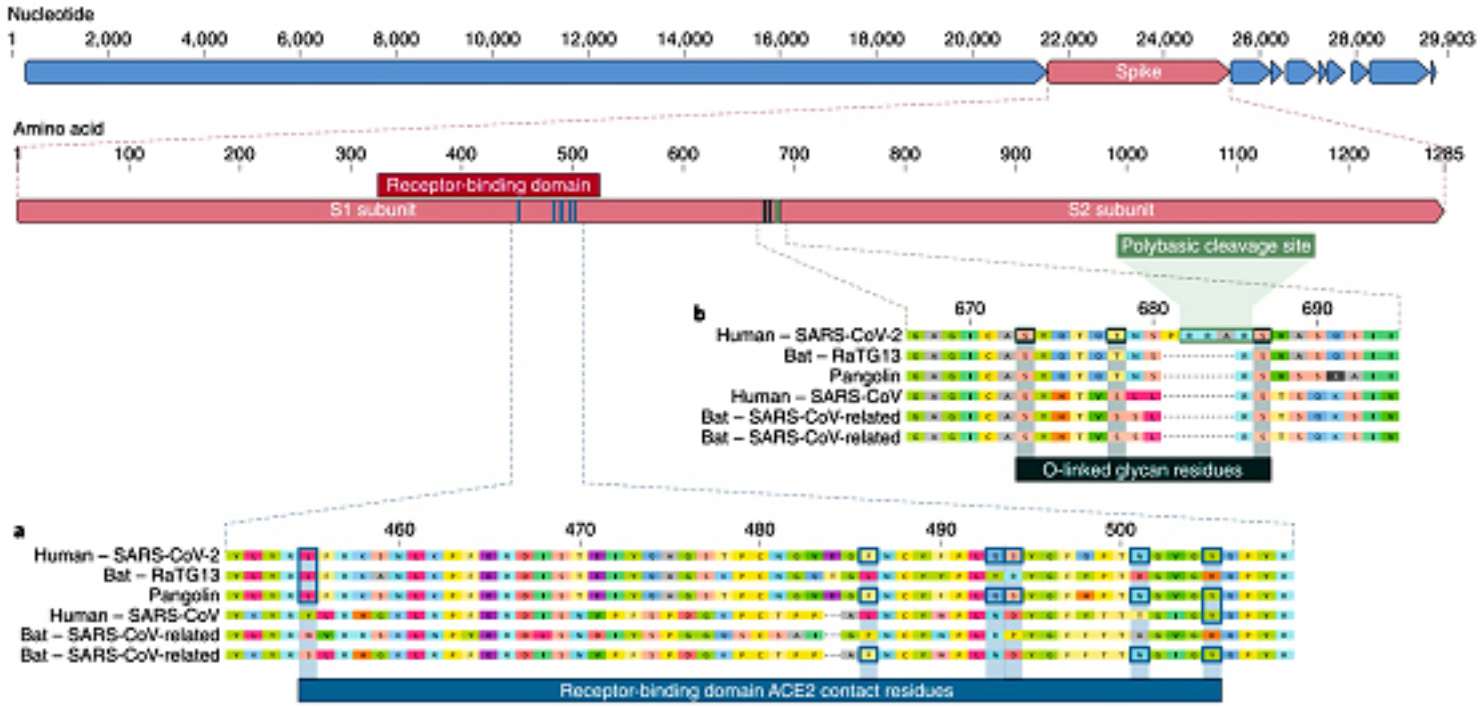
But we must mention that for ten years they have been producing Chimera Coronavirus in Wuhan, China, and therefore the data on the possibility of accidental leakage of SARAS-CoV-2 from the Wuhan Institute of Virology, the Center for the Initial Infection, remains an existing possibility that needs further research and scrutiny [29]. However, it is known that in order to perform genetic modification experiments on the emerging SARS-CoV-2 virus, researchers must use the current Coronavirus RNA as a backbone, but the available studies indicate that there are no known viruses recorded in the scientific literature that can serve as the basis for SARS-CoV-2 formation [30].

Could the emerging SARS-CoV-2 virus have been synthesised in laboratories? The scientific evidence available to us to date indicates that it is unlikely that it was synthesised in laboratories either on purpose or by accident, due to the following facts:

1) The SARS-CoV-2 genome contains several differences from previous coronaviruses along with 12 pairs of bases for introduction, and the virus with the greatest genetic similarity to it is the RaTG13 bat coronavirus, which only shares about 96% of its genome with SARS-CoV-2 (1,200 pairs of different nitrogenous bases) (Figure 2).

2) The presence of specific sites for glycosidic bonds (O-glycosidic bonds) in the SARS-Cov-2 genome, is another evidence that the virus is natural, as sugars form a mucin shield that protects the virus from attack by the immune system, and since cell cultures in laboratories do not contain an immune system, so it is unlikely that this adaptation will occur in a virus growing in the laboratory,

Figure (2): The human corona virus genome and its similarities in bats and Malayan pangolins, and also shows the presence of RBD, glycoprotein binding sites, and the Spike protein [31], [32].



and this undermines the hypothesis that the virus has multiplied from tissue culture.

3) The presence of the receptor binding domain (RBD) is very similar to SARS-CoV-2 in the Malayan Pangolin corona virus, allowing us to conclude that this may have occurred also when the virus transmitted to humans, indicating that the multiple entry founded at the cleavage site have occurred when the virus transmitted from human to human.

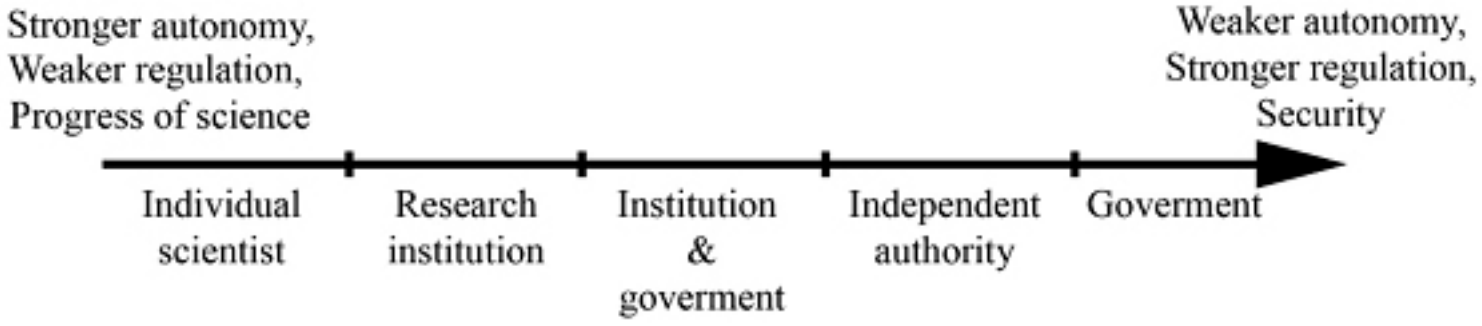
4) The RBD in SARS-CoV-2 differs from that in SARS-CoV-1 and the binding of the emerging SARS-CoV-2 virus to the ACE-2 receptor (ACE II) is not ideal, which means that there are other binding mechanisms (down "RBD" and polybasic cleavage site providing pre-activation via Furin), which resulted from natural selection, so not because of the strength of this naturally occurring process but also because of the presence of weaknesses in SARS-CoV-2 virus, all of this indicates that this virus has not been artificially modified [31], [32].

Conclusion

José Saramago said in his novel Blindness: ((*I don't think we did go blind, I think we are blind, Blind but seeing, Blind people who can see, but do not see.*)) [33], Whoever looks at what we are living today can say that, given the current development and progress in the field of genetic engineering and molecular biology, the twenty-first century will be worthy of the biological century, and there are those who say today that the First World War was chemical, while the Second World War was nuclear, and that the Third World War if it took place; would be biological [4], And we can describe the COVID-19 pandemic that the world is experiencing today due to its ferocity and its pathogenic mechanisms as a typical storm resulting from the use of an effective biological weapon [34]. Until now there is still no scientific evidence that the emerging corona virus has been synthesised or genetically modified in the laboratory, or it was intentionally spread. In the context of biological warfare, and there is no evidence proving that the virus leaked from the Wuhan Institute of Viruses in China accidentally, which are hypotheses that need proof, and that the great countries exchange accusations about the origin and source of the virus, similar to what the world witnessed during the Second World War, and it may have a background related to nationalism and intolerance, which will not be in the interest of mankind and the world. Here we have to recall the speech of doctor William Osler (one of the greatest physicians of modern times) which he addressed in 1902 to the Canadian Medical Association, speaking about "chauvinism in medicine", and according to him, "chauvinism" and "nationalism" are unforgivable sins, but at the same time he expressed his hope that because of the libertarian ideas and friendliness among nations, the worst aspects of medicine, namely "nationalism", might disappear. Long before Osler accepted the ethics of Chinese folk medicine he advocated the principle of "yi nai renshu", meaning "medicine as a way to humanity" which was founded based on the principles of Confucius, and the ancient Chinese name for medicine according to the great Tao (Way), and these ideas fall under the principle that medicine and science are not a means of glorification of a particular ethnicity, or state or nation's particular ethnicity, but rather they aim to serve the well-being of all humanity, and in the era of COVID-19, reviving such moral visions can be a vital matter for the cause of strengthening global oversight of biosafety and biosecurity [24]. and the pursuit during the fight against this virus to search for effective and safe vaccines, and ensuring coordination and cooperation for the manufacture and supply of vaccines in the production stage to meet the needs [35] also highlights the role of the 1972 Convention "Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin

Weapons and on their Destruction" as a collective action mechanism among the countries of the world, which formed the first agreement banning an entire class Weapons, as the conditions of the Cold War and the meeting of the prominent players in the international arena in both NATO and the Warsaw Pact in 1972 pushed this agreement forward and gave it a true global dimension. The international community came together to brand these weapons as "repugnant to the conscience of mankind" [36]. Therefore; the role of this agreement must be strengthened in limiting the production and storage of biological agents, and global cooperation to prevent states from resorting to biological warfare, activate monitoring mechanisms and verify compliance with their obligations, and work to include countries that are still outside it, including Israel, and also the need to impose strict control on Scientific achievements in the field of biotechnology and molecular biology that may be misused. As we refer here to the need to focus equally on Encouraging innovation in the field of biotechnology and its possession, and the importance of legislation and laws related to biosafety and biosecurity as much as possible, and supervision over compliance with mandatory biosafety and safety rules and procedures must be tightened, and researchers in the field of biotechnology must be subjected to training and educational courses on a regular basis and their credibility must be ensured. The publication of research related to biotechnology and the success in the manufacture and development of some pathogens should also be supervised so as not to be misused, in a manner that does not conflict with intellectual freedom and guarantees biological safety and biosecurity. Figure (3) shows five theoretical and practical models for decision-making ranging from an individual researcher to a complete government agency [24].

Figure 3: Five theoretical and practical models for decision-making ranging from an individual researchers to a complete government agency [24].



There may be some problems when the regulatory authorities are distributed on both sides of the left and right axis (Figure 3), where the interest of scholars or individual research institutions (on the left of the axis) is focused on developing technologies at the expense of other values, and they may also lack the skills required to assess the political, economic and ethical aspects resulting from the development of a particular biotechnology. While on the right side of the axis government agencies often lack the expertise necessary to judge rapidly changing biotechnologies, and they may overemphasize safety / social security values and strictly adhere to formal standards, thus hindering flexible case-by-case decisions. While we find, in the case of independent regulatory agencies composed of scientists, ethicists, jurists and government regulators, and due to the multiplicity of their members 'competencies, their ability to conduct a comprehensive review of new scientific research from a scientific, economic, political and legal perspective increases in a balance between safety/social security values and technical development [24].

Following the historical pattern of the interaction between war and disease, the two relatively new phenomena: unprecedented biotechnology and terrorists ready to inflict mass casualties are likely to intersect in the future, which calls for vigilance, caution and global cooperation to prevent this from happening [4].

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