Biotoxins: Invisible threat to mankind

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Biotoxins or **germ weapons** are infectious (disease-producing) agents such as **bacteria, viruses, rickettsiae, fungi, or other biological agents** – that may be utilized as weapons against humans, animals, or plants. Biological toxins are living organisms or replicating entities, and a human infected with deadly virus or bacteria could pose a threat to humans. In wars, victims of infectious diseases could become weapons themselves. Use of biotoxins by terrorists is called **bioterrorism**. Terrorists have used biotoxins in many ways; they may contain in a letter sent to you by post.

At the beginning of the recent outbreak of COVID-19, US administration accused Chinese government for experimenting and producing this corona virus in one of their laboratories situated in Wuhan City. Whatever the origin natural, accidental or intentional it is leading to unprecedented loss of lives and livelihoods globally. The question in front of us is; can we call COVID-19 a bioweapon? Ease of production and the broad availability of biological agents and technologies have led to a further spread of such biotoxins and there is an increased desire among developed and developing countries to possess and experiment up on them. As we experience it now, even an accidental release could be a real threat to mankind.

Biotoxin has a long history dating back to the siege tool of spreading infection by catapulting corpses into a fortified enclosure. In the early days of the colonies of the United States, blankets infected with smallpox virus were given to the Native Americans, and many died as a result. Many pathogens were weaponized by the great powers and tested as a warfare agent. For military use, the ideal BW is the one that is nonlethal but debilitating, and many of these have been identified. Furthermore, biotoxin is a potent anti-population tool, as exemplified by the Black Death of the Middle Ages (from 1347-1351), the Spanish Flu of 1918-1919, and the potential impact of smallpox in a population with no immunity to smallpox virus. Diseases can be separated well into two categories; (i) those that are simply infectious from the pathogen initially distributed and (ii) those that have a high degree of contagion, spreading from one human host to another as in the case of influenza, smallpox, measles and the common cold. Some diseases are largely nonlethal, but even among influenzas, the mortality can vary from well below 1% to 50%.

Biological warfare agents differ greatly in the type of organism or toxin used in a weapons system, lethality, length of incubation, infectiousness, stability, and ability to be treated with current vaccines and medicines. There are five different categories of biological agents that could be weaponized and used in warfare or terrorism. These include:

Bacteria – it is not the most harmful biological warfare agent, however, due to lack of understanding it of the severity of the infection. It can be more dangerous due to the self-replication behavior, lowest population generation time and the ability to tolerate various environmental conditions. Bacteria are single cell organisms that cause diseases such as **anthrax, brucellosis, tularemia, and plague**.

Anthrax, also called **malignant pustule**, is an acute, infectious, febrile disease of animals and humans caused by *Bacillus anthracis*, a bacterium that under certain conditions forms highly resistant spores capable of persisting and retaining their virulence for many years. Although anthrax most commonly infects grazing animals such as cattle, sheep, goats, horses, and mules; humans can develop the disease by eating the meat or handling the wool, hair, hides, bones, or carcasses of affected animals. **Plague**, an infectious fever caused by *Yersinia pestis*, a **bacterium** transmitted from rodents to humans by the bite of infected fleas. It was the disease behind the **Black Death** of the 14th century, which was the most-devastating epidemic in history.

Rickettsiae - microorganisms that resemble bacteria but differ in as they are intracellular parasites that reproduce inside cells. **Typhus** and **Q fever** are examples of diseases

caused by rickettsia organisms. **Q fever**, also called **rickettsial pneumonia**, an acute, self-limited, systematic disease caused by the rickettsia *Coxiellaburnetii*. Q fever spreads rapidly among cows, sheep, and goats, whereas in humans, it tends to occur in localized outbreaks.

This disease is usually mild, and complications are rare. Contamination of the environment leads to airborne dissemination of the rickettsiae; infection happens to persons in close contact with livestock, contaminated clothing, and other infected sources.

Fungi – pathogens that can be weaponized for use against crops to cause diseases such as **rice blast, cereal rust, wheat smut, and potato blight**. **Rust** is a plant disease caused by more than 4000 species of fungi and fungus like organisms of the phylum Oomycota. Rust affects many economically important plant species and usually appears as yellow, orange, red, rust-brown or black powdery pustules on leaves, young shoots, and fruits. In general, plant growth and productivity are commonly reduced, and some plants wither and die back. **Blight**, any of various plant diseases whose symptoms include sudden and severe yellowing, browning, spotting, withering, or dying of leaves, flowers, fruits, stems, or the entire plant.

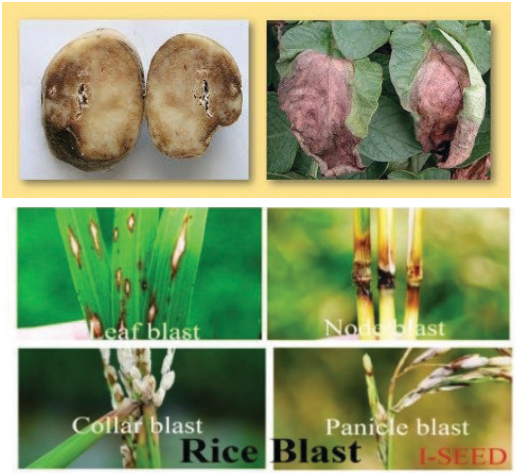

Figure 1: Potato blight and rice blast diseases

Most blights usually attack the shoots and other young, rapidly growing tissues of a plant; and many economically important plants including tomatoes, potatoes, apples, and ornamental species are susceptible to one or more blights.

Toxins – poisons that can be weaponized after extraction from **snakes, insects, spiders, marine organisms, plants, bacteria, fungi, and animals**. An example of a toxin is **ricin**, which is derived from the seed of the **castor bean**. **Ricin**, a toxic protein (toxalbumin) occurring in the beanlike seeds of the castor-oil plant (*Ricinus communis*), and one of the most toxic substances known. It is of special concern because of its potential use as a biological toxin. The most famous use of ricin as a biotoxin of assassination occurred in 1978, which was the death of Georgi Markov, a Bulgarian exile lived in London. His death confirmed that he had been poisoned by a device designed in the Soviet Union using the ricin. Ricin can enter the body through ingestion, inhalation, or injection; hence very small doses of ricin can be lethal if inhaled or injected, since these routes of exposure enable the toxin to immediately enter the bloodstream, resulting in its rapid distribution throughout the body. Ricin toxicity is based on the substance's ability to inhibit protein synthesis and to stimulate cells to undergo programmed cell death (apoptosis). Ricin is still considered to be a possible weapon of terror, and some terrorist scenarios might be the inoculation of ricin into food or water supply or the dispersal of a ricin aerosol in a confined indoor space or the sending of small quantities of ricin anonymously through postal systems.

Viruses are always communicable agents, and it is the most harmful biological warfare agent due to its size. These are obligate intracellular parasites and are generally made of a protein coating and a core containing genetic material, and about 1/100 the size of bacteria. Unlike other biological warfare agents, viruses contain both living and nonliving characteristics, and cannot survive under the normal physiological conditions; hence they are completely dependent on host cells for the replication. Most viruses contain single strand RNA except for few other viruses which contain DNA. Antiviral drugs aimed in treating viral infections are most effective during the replication of viruses as they do not have any other crucial metabolic reactions like bacteria do, which are targeted by antibiotics. The main challenge faced in prescribing antiviral drugs is that symptoms start appearing at later stages during a viral infection, and by this time most of the viral multiplication have taken place. In such an instance, antiviral drugs will have little to no effect in

controlling the disease.

Viruses can be weaponized to cause diseases such as **equine encephalitis** (Venezuelan equine encephalitis, eastern equine encephalitis, and western equine encephalitis viruses), **smallpox** (variola virus), **Russian flu, Spanish flu, Asian flu, chikungunya fever, bird flu, swine flu, Nipah virus disease, Hanta virus disease, Lassa fever, Ebola virus disease**, Middle East Respiratory Syndrome (**MERS**), Severe Acute Respiratory Syndrome (**SARS**), and **novel corona virus disease – COVID-19** (Sars-CoV-2).

Equine encephalitis is a severe viral disease that commonly affects horses and mules, and it sometimes affects birds, reptiles, and humans. Of the several strains of the virus, the most prevalent are the A group, which includes the Eastern, Western, and Venezuelan strains. The virulent Western type has mortality as high as 90% in horses and 10% in humans. Birds appear to harbour the disease but do not exhibit any definite symptoms, since mosquitoes behave as the carrier that transmit the virus from birds to horses, mules, or humans. This disease can cause permanent brain damage.

Smallpox, also called variola major, was caused by variola virus belonging to the orthopox virus genus. It was an acute infectious disease that begins with a high fever, headache, and back pain and then proceeds to an eruption on the skin that leaves the face and limbs covered with cratered pockmarks, or pox. For centuries, smallpox was one of the world's most-dreaded plagues, killing as many as 30% of its victims, most of them being children. Smallpox continued to spread until the early 19th century, when vaccination was established against it.

Chikungunya fever is a viral disease transmitted to humans by infected mosquitoes. It is often characterized by fever, headache, rash, and severe joint and muscle pain. This virus was first detected in an epidemic that occurred in 1952-1953. This fever was caused by chikungunya virus and it is debilitating, but in certain individuals can be life threatening. In infants and older adults, infection may lead to encephalitis and long-term neurological disability.

Lassa fever is a haemorrhagic fever which is caused by the **Arena virus**, and it typically occurs in West Africa. Lassa virus is transmitted to humans mainly through handling rats, food or house-hold items contaminated by rats' urine and faeces. The virus can spread between people through direct contact with the body fluids of a person infected with Lassa fever, as well as contaminated bedding and clothing.

Ebola virus disease (EVD), formerly known as Ebola haemorrhagic fever; is caused by the **Filo virus**. It is most commonly associated with bioterrorism, and is a severe, often fatal illness affecting humans and other primates. The virus is transmitted to people from wild animals (such as fruit bats, porcupines and non-human primates) and then spreads among the human population *via* direct contact with the blood, secretions, organs or other bodily fluids of infected people, and with surfaces and materials contaminated with these fluids. The average EVD case fatality rate is around 50%. It is thought that fruit bats of the *Pteropodidae* family are natural Ebola virus hosts.

Nipah virus disease - this virus is considered very dangerous due to high mortality and inability to control the disease. The highly virulent virus easily infects pigs and transmits to humans, especially those who come in close contact to them. Dogs, cats, horses are also natural reservoirs. Clinical symptoms include brain dysfunction with hypertension and tachycardia, followed by rapid deterioration which leads to irreversible hypotension and death.

SARS is caused by a coronavirus, a type of virus usually associated with pneumonia and the common cold. It is a highly contagious respiratory illness characterized by a persistent fever, headache, and bodily discomfort, followed by a dry cough that may progress to great difficulty in breathing. This appeared in November 2002 in Guangdong province, China, where it was diagnosed as an atypical pneumonia. SARS coronavirus (SARS-CoV) was transmitted to humans from an animal reservoir, believed to be horseshoe bats. Among humans the virus is transmitted from an infected person through bodily secretions, usually droplets expelled by sneezing or coughing. By the end of May 2003, more than 8000

cases had been reported, and approximately 800 people had died from the disease. Diagnosis of SARS is made after other illnesses such as pneumonia and/or influenza are ruled out and a history of the patient's movements has established the likelihood of exposure to an infected person. Since no specific medication is available against the SARS coronavirus, treatment is usually restricted to easing the patient's symptoms until the illness has run its course. By June 2003 the contagion had been controlled to the point where restrictions were eased.

MERS is an acute viral respiratory illness that is characterized primarily by cough, fever, and shortness of breath and is sometimes associated with severe and potentially fatal complications such as pneumonia and kidney failure. This is caused by a coronavirus known as MERS-CoV, which attacks the respiratory system. The illness was first observed in June 2012 in Jeddah, Saudi Arabia, and soon afterward it was reported in other countries in the Middle East. Later, it was detected in European countries, North African countries, and in countries more distant from the Middle East, including China, Malaysia, South Korea, and the United States. This shows that MERS had the potential to escalate into an international public health emergency. More than 60% of infected persons who developed serious illness required hospitalization, and individuals died in more than 30% of the reported cases. Close contact is thought to be the primary means of disease transmission among humans. Similar to the SARS-CoV, MERS-CoV also has a very large RNA genome. Bats are a suspected natural reservoir of coronaviruses, and genomic analyses showed that MERS-CoV is closely related to coronaviruses derived from bats. However, research has indicated that infection with the virus may be widespread among camels in the Middle East and Africa. The high likelihood for direct or indirect human contact with camels in those regions suggested that camels were a probable source of human infection. Yet, there is no clinically proven therapy for MERS-CoV; thus, symptomatic treatment and supportive care is given to patients.

COVID-19

In November 2019, Chinese researchers identified a novel coronavirus, subsequently named severe acute respiratory syndrome coronavirus 2 (**SARS-CoV-2**), **COVID 19**, which had been isolated from a patient with severe pneumonia who was hospitalized in Wuhan City, Hubei province, China. By the end of August 2020, infection with COVID-19, had been confirmed in more than 25,384,000 individuals around the world, where more than 850,590 died and over 17,493,850 recovered (see Table 1)

Table 1: Situation of Coronavirus disease, by country, as at end August 2020.

Country	Total confirmed cases	Total deceased	Total recovered
USA	6,173,236	187,224	3,425,723
Brazil	3,862,311	120,896	3,031,559
India	3,619,169	64,617	2,772,928
Sri Lanka	3,012	12	2,860

In addition, millions of people's lives have been affected as a result of mandatory isolations or quarantines. Novel finding of the COVID-19 is that it contains a collection of various types of corona viruses derived from bats, including the SARS and MERS coronaviruses as well. The novel virus shared 79% of its genome in common with a previously reported SARS coronavirus originally isolated from bats, which raised concerns that COVID-19 represented a global disease threat, which is most similar to the SARS coronavirus.

This virus currently spread to more than 216 countries around the world. Coronaviruses (CoVs) are relatively large spherical viruses containing a single-stranded positive-sense RNA (+ssRNA) genome encapsulated within a membrane envelope. The viral membrane is studded with glycoprotein spikes that give coronaviruses their crown like appearance. SARS-CoV-2 viral pathogens bind to the human angiotensin-converting enzyme-2 (ACE-2) receptor through these glycoprotein spikes.

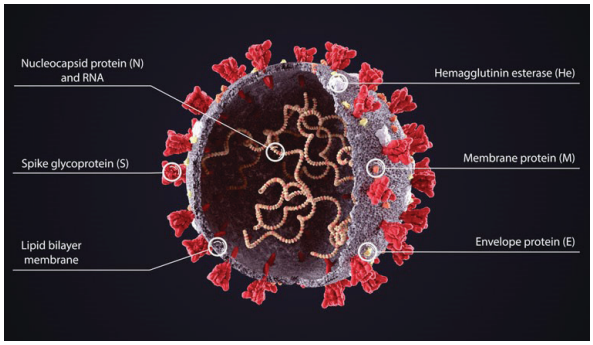

Figure 2: Schematic diagram representing structure of SARS-CoV-2

According to the novel findings, ACE-2 gene is actively expressed the goblet cells and club cells found in the bronchial epithelium of current smokers and non-smokers, respectively. While corona viruses infect both humans and animals, certain types of animals such as bats that host the largest variety of coronaviruses appear to be immune to coronavirus-induced illness. The SARS-CoV-2, SARS-CoV and MERS-CoV can be classified under the beta-coronavirus class; since all these viruses attack the lower respiratory system to cause viral pneumonia. Furthermore, SARS-CoV-2 may also affect the gastrointestinal system, heart, kidney, liver, and central nervous system leading to multiple organ failure. Current information indicates that SARS-CoV-2 is more transmissible and contagious than SARS-CoV. Transmission of the SARS-CoV-2 virus occurs via respiratory droplets released by coughs and sneezes within a range of six feet, which comes in contact with another person's mouth or nose, seldom through eyes. This virus is capable of surviving on different surfaces with a life span ranging from hours to days. Therefore, the threat of contracting the virus is extremely high, and the cure still being unknown, prevention remains to be the best opinion at this time.

To date, there are no SARS-CoV-2 specific antiviral agents, but researchers have been racing to discover possible treatments and effective therapeutic agents to save lives and produce safe vaccines for future prevention. Researchers are testing 36 vaccines in clinical trials on humans, and at least 89 preclinical vaccines are under active investigation in animals. But Russia and China have already approved one vaccine each, without waiting for the results of phase III clinical trials, which are being planned to be done now.

An economic and efficient therapeutic strategy is to repurpose existing drugs, due to the costly, lengthy and arduous process of new drug development. Thus, scientists have been able to rapidly respond with a suggested list of existing drugs with therapeutic potential for COVID-19, which are mentioned below;

- **Baricitinib** - proposed due to its anti-inflammatory effect and possible ability to reduce viral entry. A fixed dose of the anti-HIV combination, **lopinavir-ritonavir**, is currently in clinical trials with **Arbidol** or **ribavirin**.
- **Remdesivir** - previously tested in humans with Ebola virus disease and has shown promising results in animal models for MERS and SARS. This drug is currently being studied in phase III clinical trials in both China and USA.
- **Favipiravir** - a purine nucleoside leading to inaccurate viral RNA synthesis and has recently been approved for a clinical trial as a drug to treat COVID-19.
- **Chloroquine** - an antimalarial drug that has proven effective in treating coronavirus in China.

Since there is limited clinical and basic research information at this time, treatment options for COVID-19 currently comprise of investigational drugs and management of symptoms.

The ripple effect of the COVID-19 outbreak could potentially bring major challenges to worldwide health systems and have far-reaching consequences on the global economy if the spread of the virus is not effectively controlled. Therefore, a concerted effort to develop effective drugs and vaccines against existing and potential future coronavirus infections and other highly pathogenic virus outbreaks is necessary to reduce overwhelming impacts on human life and worldwide healthcare systems.

Prevention of future global pandemics

We are hopeful, under the terms of the Biological Weapons Convention (BWC), member states are prohibited from using biological weapons in warfare and from developing, testing, producing, stock- piling,

or deploying them. However, there are instances of acquiring and using of biotoxins by terrorists. Indeed, in such situations, misuse of potential bioweapons was responsible for spreading of diseases, which caused more deaths than reported, though they have not been consciously used as bioweapons. Now it is high time that the UN and WHO carried out proper monitoring and enforcing stringent guidelines in order to handle the consequences of a global pandemic more effectively, and to prevent the occurrence of such an outbreak in the future.

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