No More Pandemics

No More Pandemics:

Toward a World Free from Infectious Diseases

By

Hiroshi Kase and Yoshikazu G. Mikawa

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HIGHLIGHT

- ✧ This book proposes a concrete path to bring an end to pandemics and achieve a world without infectious diseases, suggesting an escape from the long history of infectious diseases that have brought misery and confusion to humanity.

- ✧ If no one gets infected, there can be no pandemic. Therefore, to begin with, a detailed description of "methods to avoid infection" from respiratory infections (such as COVID-19, colds, influenza, pneumonia, rubella, etc.) is provided. The key point is the method of releasing aerosols produced from breathing, which continue to float indoors, to the outside through ventilation. This is crucial because aerosols in the exhaled breath of infected individuals contain pathogens like viruses. If ventilation is even slightly inadequate, the risk of airborne transmission increases for individuals present in the same indoor space.

- ✧ Furthermore, by maintaining ventilation to keep indoor CO_2 concentrations, which accumulate along with aerosols through breathing, below 1,000 ppm, it has been demonstrated that the probability of airborne transmission can be significantly reduced. This establishes a method to prevent infection.

- ✧ If all indoor spaces where people gather are consistently supplied with fresh air through ventilation, respiratory infections will come to an end and disappear in any region. Alongside such air-quality measures, improving water environments (drinking water, toilets, sewage) would eliminate gastrointestinal infections such as cholera and plague.

- ✧ Creating cities and nations with such indoor environments requires extensive costs and efforts. However, if everyone collaborates, the returns can be immeasurable in terms of not only economics but also societal, cultural, and individual health and safety. This endeavour can fundamentally address the crises and stagnation faced by modern society, including global environmental concerns, population issues, ageing demographics, challenges in healthcare administration and funding, poverty, and more. It paves the way towards a sustainable and promising future.

INTRODUCTION

There has always been the hope that infectious diseases would eventually be conquered by advanced scientific technologies. When the World Health Organisation (WHO) declared the eradication of smallpox in 1980 it was thought that this moment had arrived. (Smallpox is the disease that has afflicted mankind more than any other dangerous pathogens.) Unfortunately, the solution had still not been found. Once again hopes arose in the following year, 1981 when the incidence of polio (paediatric paralysis) in Japan was eliminated.

The Present Situation

The global pandemic of the New Coronavirus (SARS-CoV-2), which began in January 2020, attacked countries all around the world. Wave after wave of infection besieged us. Even now, three years later, significant damage is still being done.

According to the Johns Hopkins University, which is compiling data on the New Coronaviruses, as of January 2023 (the third year of the pandemic), the total number of people infected worldwide by the pandemic had reached approximately 669 million. Of this number, about 6.8 million died.[1] The World Health Organisation (WHO) estimates the "Excess Mortality" to be 14.83 million. Excess mortality is defined as the difference between the reported total number of deaths during a crisis and an estimate of the expected total number of deaths during the same period if the crisis had not occurred. COVID-19's excess mortality accounts for both the total number of deaths directly attributed to the virus as well as the indirect impact, such as disruption to essential health services and/or disruption of the required medical care.[2]

A potent vaccine to control this latest pandemic, using the latest science and technology was developed at an unprecedented speed.[1] More than 13.2 billion doses of vaccine were administered worldwide.[3] However, as a result of the repeated emergence of new mutant strains and successive waves of new variants, the New Coronaviruses increased the resistance of our immune systems. These had already been boosted by the vaccine and by already existing epidemic strains.[4] The vaccine strategy thus became a never-ending game fighting the immune-escape ability of the New Coronaviruses.

The pandemic has had a profound impact on politics, economics, education, health and well-being, gender equality, workplaces, mobility, relationships and families.[5] The pandemic crisis has also jeopardised the world's commitment to the Sustainable Development Goal (SDGs)[6] of 2030. For the last 32 years, the United Nations Development Programme (UNDP) has used the Human Development Index (HDI) to assess the health of nations. Despite a consistent upward trend in HDI, the index experienced a decline in two consecutive years, 2020 and 2021.[7]

As the COVID-19 pandemic persisted and the measures taken to control it became commonplace, many people fell into states of extreme negativity, despair and resignation. Social fragmentation was brought about by lockdowns, mandates and the differing opinions and policies regarding COVID-19 vaccines in various countries, which created divisions and tensions among communities.

In late 2022/early 2023, politicians in regions where the Omicron strain was predominant began to move towards significant deregulation. This move was encouraged by research findings suggesting that infection rates were falling, and that people infected with the Omicron strain were less likely to become seriously ill. For example, in the UK, after a positive test, all legal restrictions, such as the wearing of masks in public places, and self-isolation, were removed. [8]

The history of mankind has been marked by a succession of infectious diseases which have repeatedly spread worldwide. The New Coronavirus pandemic is the fifth that has occurred. It caused 14.83 million deaths; the Black Death in the 14th century caused 200 million; smallpox in the 16th century caused 56 million; the Spanish flu in the 20th century 40–50 million; and the Plague of Justinian in the 6th century in the Eastern Roman Empire 30–50 million. All of the figures above are excess mortality deaths. [9][10][11] Certainly, the numbers have decreased, but people continue to die in large numbers.

Despite significant advances in science and technology related to the production of vaccines and the use of many advanced remedies for viruses, the approach to pandemics has essentially not changed much in the last 2,000 years.

Why?

It has become clear that unless we change something basic in our response to pandemics, it is inevitable that one pandemic after another will attack us time and time again, each time with great loss of life and huge damage. Moreover, today, the rate at which epidemics and pandemics spread around the world is accelerating because of the increased movement of peoples, and the increasing trade in animals and animal-derived foods.[9] The future of humanity itself is in danger if the current response is not changed in some way.

In an attempt to avoid this tragedy, many countries are considering post-corona measures. In 2022, a to End COVID-19[chapter 1, ref. 15] was proposed by a committee of 386 researchers, clinicians and policy advisers from 112 countries. Their objective was to discuss a list of proposals such as, "Social and Health actions to be taken to end the COVID-19 threat". The committee considered the evidence that vaccines are an effective way of combating COVID-19. However, vaccines alone will not be able to bring an end to the threat to public health. After prolonged discussion, the committee proposed the concept of "Vaccines Plus", which would combine preventative infection measures, advanced treatments and government incentives, together with ongoing vaccination.

It is true, mainly in Western countries, that the latest pandemic was not controlled by a strategy based on vaccination. The reason for adding preventative infection measures to "Vaccines Plus" is based on the fact that the New Coronavirus is an airborne virus with a high risk of indoor transmission. The closing statement from this consensus clearly confirmed that the initial response failed to address the airborne nature of the New Coronavirus. The statement also clearly calls for governments to stipulate specific preventative structural measures such as ventilation and air filtration systems, giving the highest priority, particularly to communal spaces, such as the workplace, educational institutions and commercial centres.

While the idea of ending the pandemic was part of the Multilateral Consensus, no specific plan for ending the pandemic was proposed. This was because the analysis of the underlining cause of the pandemic was considered beyond the scope of the study.

Looking back at the history of infectious diseases, we can see that every infectious disease has forced people to live in coexistence with pathogens. As a result, we have been forced to continue to contend with infectious pathogens. An outbreak ceases and then, in time, settles down, but the original cause of the outbreak has not been clearly understood. Once again, the next infectious disease strikes, and then, once again, we have the same pattern repeated. Many experts around the world have learned from this history and argue that coexistence is the path we should take. Therefore, they recommend that we continue to fight against pathogens, accept living in coexistence, use weapons such as vaccines and therapeutic drugs, cooperate with the medical institutions, and simply wait for the infection to subside.

Insufficient measures taken to prevent the spread of the virus so far have contributed to the current pandemic situation. Coexistence with the virus is established once an individual is infected. This state of coexistence is inevitable and must be addressed to prevent the recurrence of such a devastating outcome. We must implement fundamental reforms in how we manage the consequences of coexistence to ensure the survival of humanity in the face of viral threats. Research has shown that pandemics typically begin with an initial infection in an individual. It is of the utmost importance for us to find a way of avoiding infection in the first place.

Non-infectious measures have been used in the past to bring an end to waterborne pathogen infections such as *Vibrio cholera*. During that time, the level of scientific understanding and technological capabilities was not sufficient to provide a detailed explanation for why these infections were brought to an end through non-infectious measures. However, WHO is launching a Water, Sanitation, and Health (WASH) programme in developing countries, and is campaigning for safe and clean water sources, effective sanitation infrastructures, and good hygiene practices. This programme has already begun to produce positive results[12].

Thanks to significant scientific and technological advances, we now have the tools and knowledge necessary to more effectively prevent and control pandemics. We have the potential to significantly reduce their impact and move closer to a pandemic-free world that has never, until now, been realised.

Therefore, in Chapter 1, we will analyse in detail why the pandemic could not be brought to an end. Based on this analysis, in Chapter 2, we will present methods to prevent infection. Finally, in Chapter 3, we will reveal a method and process for sustainably bringing an end to any pandemic. This proposal can be considered the first of its kind in history.

In Chapter 4, we will describe the process of creating indoor environments that are free from respiratory infections, including SARS-CoV-2, as well as specifying the appropriate buildings, renovations, equipment, and operational systems.

Additionally, we will mention the costs associated with this global undertaking and the benefits that can be obtained through its realisation.

Time is running out to prevent future pandemics caused by emerging or re-emerging pathogens. Even after the COVID-19 pandemic is contained, the risk of future pandemics remains high. However, we believe that by implementing "non-coexistence" measures, we can mitigate this risk and work towards a pandemic-free world.

The challenge to eradicate future pandemics must be confronted now.
Our aim in this book is to present the answer.
Our time is up. Let us aim for NO MORE PANDEMICS!

1. PERSPECTIVES ON AN END TO PANDEMICS

Pandemics occur because people are infected by pathogens, organisms that cause disease. If people were not infected with pathogens, pandemics could not occur. Pandemic history is the history of combating infection spread. However, until recently, it was impossible to know how to avoid infection caused by pathogens. Therefore, we can say that up until the last few years, we had no other choice but do our best to continue the fight against the spread of infection. But, in fact, we were fighting a losing battle. Once the infection had arrived, we were just struggling to contain its spread. The truth is that before the arrival of vaccines, infection was uncontrollable.

In "The Role of Ventilation in the Prevention of Pandemics" we intend to trace the history of infectious diseases and the development of related science and technology. We will explain why infection prevention was previously impossible and will inquire if this possibility is currently feasible. Our approach is to explore Infection Control Strategies to find a solution.

1.1 Infectious Diseases History and the Related Science and Technologies[9,10,11,12]

Until just 160 years ago, not only microorganisms but also insects, frogs, and even rodents were believed to be lower life forms. It was presumed that microorganisms appeared spontaneously if the appropriate conditions of temperature and proper nutrition were available.

However, in 1861, our understanding of the arrival of these microorganisms changed when Louis Pasteur in France showed experimentally that microorganisms etc. did not, in fact, come into existence spontaneously.

After Pasteur's non-spontaneous generation theory was established, a great deal of research was carried out on the relationship between disease and microorganisms. Scientists gained a deeper understanding of infectious diseases, which, at that time, were called "epidemic diseases". In the late 19th century Robert Koch discovered anthrax, tuberculosis, and cholera bacilli in Germany. He then produced the anthrax vaccine. Following this, Alexander Yersin and Shibasaburo Kitasato discovered the *Plague bacillus*; and Kiyoshi Shiga discovered *Shigella dysenteriae*. From this time on, bacteriology became the mainstream of cutting-edge science and led to the discovery of numerous pathogens.

Regarding infectious diseases, the Cuban physician Carlos Finlay discovered in 1881 that mosquitoes transmit the particle responsible for Yellow Fever. As a result of his discovery, there was a dramatic reduction in the spread of the disease. His discovery brought about the destruction of the mosquito breeding grounds and the far-reaching eradication of mosquitoes. The extermination of mosquitoes in Central America was an important factor in the building of the Panama Canal. Later, in 1928, Max Tyler isolated the Yellow Fever virus from a Yellow Fever patient. An attenuated strain from his Yellow Fever patients was used for vaccination against this disease.

In 1933, in a ground-breaking discovery, it was discovered that a virus, the influenza virus, caused the Spanish flu pandemic (1918–1919). People incorporated strategies such as wearing masks and washing hands into their daily lives without actually understanding the cause of the pandemic. These same strategies have been used worldwide for the New Coronavirus over 100 years after the discovery of the virus.

New horizons in the use of drugs in the treatment of infectious diseases were opened up with the discovery of the antibiotic penicillin by Alexander Fleming (1929), the discovery of the syphilis drug Salvarsan by Paul Erlich and Sahachiro Hata (1910) and the synthesis and development of sulfa drugs by Gerhard Domagk (1935).

The discovery of penicillin opened the door to a golden age in the quest to discover new antibiotics from natural compounds. Natural compounds and semi-synthetic derivatives of these antibiotics were commercialised and introduced into clinical practice. Many bacterial infections that had plagued mankind since ancient times were now treated with the "silver-bullet wonder drug" of antibiotics. As a result, the number of deaths from pneumonia, gastroenteritis, and other infectious diseases declined sharply after World War II. However, by 1942, the same year as the introduction of penicillin G, actually penicillin-resistant *Staphylococcus aureus* (MRSA) had already been identified. Methicillin was developed as an effective antibiotic against this resistant strain. In 1961, methicillin-resistant *Staphylococcus aureus* was first reported. It spread rapidly throughout the world in the 1970s, and vaccination was used to prevent its spread.

Tuberculosis is known to have existed since prehistoric times; traces of lesions having been found on mummies. By the end of the 19th century, the disease was endemic in Europe and North America. The introduction of streptomycin, discovered by Selman Waxman in actinomycetes, and later the BCG vaccination programme developed by Albert Calmette and Camille Grand caused a significant drop in Tuberculosis cases.

In spite of all the progress, the fact is that viral infections do not respond to antibiotics and still rely heavily on the patient's own immunity. Respiratory infections are airborne in origin thus they were transmitted more and more easily in the 20th century, as cities grew larger and more densely populated. In the 1950s, virus isolation and detection methods were improved, and several important human respiratory infection viruses were identified. These include the varicella-zoster virus, the measles virus, and the rhinovirus which causes the common cold.

The invention of the electron microscope (1931) by German scientists Max Knoll and Ernst Luska made it possible to observe viral morphology. By the 1950s, after the double helix model presented by Watson and Crick in 1953, a substantial amount of knowledge about DNA and heredity mechanisms had been accumulated and the functioning mechanisms of viruses became more apparent.

In the 1960s, many more viruses were discovered, including the hepatitis B virus. The key enzyme, reverse transcriptase, used by retroviruses to synthesise DNA from RNA was independently discovered by Howard Martin Temin and David Baltimore in 1970. This discovery was pivotal in developing antiviral drugs and represented a significant milestone in the history of viral infections.

New viruses and virus strains continued to be discovered in the 21st century, prompting the identification of new viral infections such as SARS and Nipah. And then the pandemic of the New Coronaviruses arrived in 2020!

1.1.1 Technologies for inspection and tracking/monitoring[11]

In 1977, the British biochemist Frederick Sanger and his colleagues developed a "dideoxy" chain-termination method for sequencing DNA molecules. To date, this still remains the gold standard method for determining DNA sequences along with the next-generation sequence (NGS) technology. Next-generation sequencing (NGS) is a modern high-throughput DNA sequencing technology that enables the rapid sequencing of large amounts of DNA samples in a cost-effective manner.[18] It allows for the sequencing of millions of DNA fragments simultaneously, providing researchers with unprecedented access to the entire genome of an organism or a particular gene of interest. The concept of the NGS was initially developed at Lynx Therapeutics[18] and further refined at Illumina, 454 Life Science, Ion Torrent and Pacific Biosciences (PacBio). NGS has played a critical role in the analysis of the SARS-CoV-2 virus since the start of the pandemic. The technology has been used extensively to sequence the genome of the SARS-CoV-2 virus providing valuable insights into its origin, evolution, and spread.

The nucleic acid amplification technology, widely known as PCR (polymerase chain reaction), was invented by Kary Mullis in 1983. This technology uses a thermophilic DNA polymerase to amplify a small amount of DNA template exponentially, generating millions or billions of copies of the target sequence within an hour or so. PCR has become a widely used method in molecular biology and has many applications, including the diagnosis of infectious diseases, genetic testing, and forensic analysis. PCR has been a critical tool in the analysis of SARS-CoV-2 because it allows for the rapid and accurate detection of the virus. It contributed to the identification of the number of infected people and was used to analyse their results and to make judgements on actions to be taken. In some countries, a very large number of people were PCR tested and PCR data were used to control infection. For example, in South Korea, PCR testing was quickly implemented on a large scale after the first cases of the new Coronaviruses occurred. Surveillance of persons in close contact with patients who tested PCR positive was carried out. This was effective in controlling infections. Nevertheless, this infection control measure, known as the "K quarantine method" also resulted in a delayed spread of the disease.

1.1.2 Genome analysis technology[2]

DNA sequencing has made rapid progress because of the advance in technological developments. The Human Genome Project led by Francis Collins of the National Institutes of Health (NIH) and Craig Venter of the Celera Corporation had made it possible to sequence the entire DNA of the human genome by 2003 in the US. It took about 13 years to analyse the entire human genome; the same results could be obtained in just one day by 2021.

This has enabled the coronavirus genome (RNA consisting of approximately 30,000 bases) to be sequenced rapidly in a large number of specimens. Therefore, the analysis of mutations and the spread of viral infection, as well as the epidemiological tracking of the virus became possible. As a result, fundamental data essential for various fields were obtained. All of the above greatly contributed to the development of strategies to combat a pandemic such as the new Coronavirus.

1.2 Influenza and SARS-CoV-2 Infections[3]

1.2.1 Influenza[3]

Influenza is a respiratory tract infection caused by the influenza virus and is a serious illness that is distinct from the common cold. Influenza occurs annually in many parts of the world, peaking in January and February in the Northern Hemisphere and in July and August in the Southern Hemisphere. Influenza viruses come in three types: A, B, and C. The most prevalent types are A and B. They contain glycoproteins called haemagglutinin (HA) and neuraminidase (NA) on the surface of the particles. Our immune system targets those specific antigens to protect against infection. By recognising these foreign antigens, the immune system is able to mount a response to eliminate the virus and prevent further infection.

Influenza A pandemics occur every few years and a particular strain can continue for several decades, where a different subtype of the virus suddenly emerges and replaces the previous subtype. In 1918 the Spanish Flu, caused by the unknown Spanish influenza virus H1N1, emerged and preserved for the next 39 years. As mentioned previously, the Spanish flu is estimated to have affected 600 million out of the world's population of 1.8 billion, while 20–40 million people died in Japan alone. In 1957, the Asian flu (H2N2) broke out and lasted for 11 years. This was followed by the Hong Kong flu (H3N2) in 1968, and then the Soviet flu (H1N1) in 1977.

At the moment, three types of influenza viruses exist, A-type H3N2, A-type H1N1, and B-type are prevalent worldwide. However, a different kind of influenza pandemic struck the world in 2009. Many people were shocked by the fact that this new virus originated from swine, rather than the usual seasonal flu strain.

The treatment of influenza is mainly based on the administration of antiviral drugs. Neuraminidase (NA) inhibitors (Relenza®, Tamiflu®, Rapiacta®, Inavir®, etc.), which came into use in the 2000s, are effective against both type A and type B influenza, and if taken within two days of the onset of illness, can reduce symptoms and shorten the duration of illness. On the other hand, resistance to neuraminidase inhibitors has emerged and this is an issue of great concern. The antigenic properties of haemagglutinin (HA) and NA of the influenza virus change slightly due to the accumulation of mutations in the viral genes even within the same subtype. This is known as continuous antigenic drift and it occurs frequently with influenza viruses, which is why seasonal epidemics repeat every year. Influenza remains the largest infectious disease in the human population.

There are some basic rules that can help prevent influenza. The first recommendation is to avoid crowds during an influenza epidemic. If it is impossible to avoid crowds, it is recommended that people take preventive measures such as wearing a mask, gargling, and washing their hands when they come from outside. The current influenza vaccine (inactivated HA vaccine) does not guarantee that an individual will not be infected. However, it has been proven effective in blocking the onset of influenza (efficacy rate is around 60%) and in preventing severe illness and complications.

1.2.2 SARS-CoV-2 infection

SARS-CoV-2 is believed to have originated in bats and is transmitted to humans via an intermediate host[4]. SARS-CoV-2 infections (COVID-19) can be asymptomatic (in up to 40% of cases) or they can cause a wide variety of illnesses ranging from mild symptoms to life-threatening diseases. Symptoms reported by infected patients include fatigue, cough, fever, headache, runny nose, sore throat, muscle ache, and various other symptoms such as an abnormal sense of taste and an abnormal sense of smell, and also diarrhoea. Common complications in hospitalised patients include pneumonia, acute respiratory distress syndrome (ARDS), acute liver failure, cardiac problems, thrombotic coagulopathy, acute renal failure, as well as various neurological symptoms.

Patients with severe symptoms may also develop an out-of-control interferon response (cytokine storm) and macrophage activation syndromes. Comorbidities such as hypertension, diabetes, cardiovascular disease, chronic lung disease, chronic kidney disease, malignant tumours, and chronic liver disease are also found in 60–90% of hospitalised patients. Overall, the mortality rate of patients hospitalised with COVID-19 is about 15–20%, but it can be as high as 40% for patients requiring ICU admission. The estimated global mortality rate ranges from 0.25% to 3.0%, with higher rates for older patients; 0.02% for those aged 20–49 years; 0.5% for those aged 50–79 years; and more than 5.4% for those aged 80 years and older. The symptoms presented by children are primarily limited to the upper respiratory tract. However, rare multisystem inflammatory syndromes have been reported. Patients with life-threatening COVID-19 have shown an impaired type I interferon response, which can lead to a cytokine storm.

In most countries, multiple public health strategies were implemented from the early stages of the pandemic. These included individual personal actions (e.g., social distancing, hand washing, mask use, cough etiquette); cluster identification (e.g., identification of cases, contact tracing, isolation); regulatory strategies (e.g., school closures, workplace closures, curfews, closures, restrictions on public transport, and limits on the size of gatherings); national and border closures (e.g., travel restrictions and mandatory quarantines).

While waiting for the development of safe and effective vaccines and treatments, the goal of these public health strategies was to slow down and flatten the epidemic curve, prevent medical crises, and protect those who were most vulnerable to serious illness.

1.2.3 Vaccines for SARS-CoV-2

One of the most remarkable scientific achievements in history has been the rapid research, clinical testing, and production of a vaccine for the SARS-CoV-2. Less than a year after the pandemic started, the vaccines became available based on a new platform that utilises messenger RNA (mRNA) coding for viral spike proteins. These vaccines were developed and produced by Moderna in the United States. and Pfizer/BioNTech in Germany. In addition, a virus vector vaccine was developed in collaboration between AstraZeneca and the University of Oxford in the UK. The speed of the development of the vaccine was so fast that it completely overturned the conventional understanding of vaccine development. The rapid development of these vaccines was made possible due to the accumulation of about 30 years of previous research and technology by many researchers, as well as the enormous financial support provided for their development.[5] Without this support, the entire development process would have been at risk.

These vaccines require two or more doses to achieve immunity and have been reported to reduce the risk of developing New Coronavirus infections (symptoms such as fever and a positive PCR test) by 95.0% (Pfizer), 94.1% (Moderna), and 70.4% (AstraZeneca). In addition, all vaccines can prevent severe or asymptomatic infections by 80–90% or more[6]. The New Coronavirus vaccine has been administered in 233 countries and regions. The total number of vaccine doses worldwide exceeded 12,885,430,000 doses as of 27 October 2022. While some developed countries, Japan, for example, invested huge sums of money to ensure the availability of vaccines, many developing countries, with less economic power, lagged behind. This resulted in an unequal distribution of vaccines around the world.

A distinctive feature of a New Coronavirus pandemic is the repeated appearance of new variants. This happens because the New Coronaviruses acquire mutations that allow them to escape the host immune system already established by existing and/or prior epidemic strains and vaccines, i.e., immune escape.[7, Introduction ref 4] During successive waves of epidemics, immune-evading subtypes and recombinants (BA.1, BA.2, BA.4, BA.5, XBB.1.5., BQ.1) emerged, which were able to evade the immune response.[8]

As the efficacy of previous vaccines in preventing infection and neutralising activity against the new variants was weakened[9], an mRNA vaccine against the Omicron sub-strain was designed, developed, and made available for additional vaccination in a short period of time. The US Centers for Disease Control and Prevention (CDC), in December 2022, announced the effectiveness of this vaccine in preventing hospitalisations. The risk of hospitalisation due to severe symptoms of Omicron infection was about 40% lower in those who received this vaccine than in those who had received the previous vaccine five to seven months earlier. Many countries, including Japan, are now offering additional doses of Omicron-responsive vaccines.

1.2.4 Drugs for the treatment of New Coronaviruses[10]

While the development of a New Coronavirus vaccine made the headlines, the development of therapeutic drugs also proceeded at a rapid pace. The main pathological phenomenon of New Coronaviruses is believed to be rapid viral replication during the first few days after onset, and the inflammatory response resulting from the host immune system for up to seven days after the onset. Therefore, it is important to administer antivirals or virus-neutralising antibodies early in the onset of the disease (a state where oxygen inhalation is not necessary before the onset of pneumonia). Anti-inflammatory drugs such as Dexamethasone and Tocilizumab may be important for treating moderate or severe disease after about seven days from onset, as the disease tends to gradually weaken.[10]

Antiviral drugs, such as remdesivir, molnupiravir (RNA polymerase inhibitors), and nirmatrelvir/ritonavir (protease inhibitors), inhibit the virus reproduction in the cells and therefore inhibit their growth and spread. The intravenous infusion Veklury® (remdesivir) and the oral (drinkable) medication Lagevrio® are also used for treating COVID-19. Paxlovid Pak® and Xocova ® are also antiviral drugs. There are concerns that antiviral drugs may be less effective against mutant strains of viruses due to drug resistance. A reduction in drug efficacy with remdesivir and other drugs are also reported in the literature review for surveillance purposes.[se11]

On the other hand, neutralising antibody drugs work by preventing the virus from infecting cells by antibodies recognising the surface of the virus. There are several types of neutralising antibody drugs, including Lonaprieve® (casirivimab and imdevimab) and Zebudi® (sotorovimab), which are intravenous infusions. There is also Evusheld®, which is an intramuscular injection. Neutralising antibodies are characterised by high specificity for their targets. The mutant strain has many base substitutions in the viral genome and led to many amino acid substitutions and deletions in the spike glycoprotein. Several amino acid substitutions in Omicron are located at or near the antigenic sites of these neutralising antibodies. All of the neutralising antibodies tested have been reported to have attenuated virus-neutralising effects against the Omicron BA.1, BA.2, BA.4, and BA.5 sub-variants, as evaluated *in vitro*. Thus, in the case of neutralising antibody drugs, it is necessary to develop new and specific antibodies recognising the altered epitope presented on the mutant strain.

Severely ill patients develop a systemic inflammatory response resulting in lung injury and multiple organ failure. Existing drugs such as Dexamethasone, a Janus kinase (JAK) inhibitor, Baricitinib, and Tocilizumab (Actemra), an IL-6 receptor monoclonal antibody, which is used for Rheumatoid Arthritis, have shown efficacy in severely ill patients with new strains of Coronas.

1.3 Why the Pandemic Has Not Come to an End

In the history of pandemics, there have been a few occasions in which infections have been terminated. One of the reasons for this may have been the success of herd immunity.

For example, the worldwide influenza pandemic that began in 1918[12] infected more than tens of millions of people and raged until it finally came to an end by the Spring of 1920. This is thought to be due, in part, to the fact that many people who were infected acquired neutralising antibodies against the influenza virus.

The transmission of the Spanish flu virus to immunised humans came to an end in the 1920s. However, those same viruses continued to evolve in pigs, and, in time, the link between the H1N1 strain of the Spanish flu and the virus that caused the influenza pandemic in 2009 was identified. While it’s true that some influenza viruses can persist in animals, including pigs, for many years, the causes of the 2009 influenza pandemic were likely to be more complex. The pandemic was caused by a novel strain of the H1N1 influenza virus that emerged through reassortment, a process in which two different influenza viruses infect the same host cell and exchange genetic material. This new virus was able to spread rapidly because it was a novel strain to which most people had no immunity. The pandemic was repeated because the descendants of that virus remained in living organisms on the Earth even after 100 years.

Currently, several studies indicate that the long-lived memory B cells in bone marrow exist as one of the major mechanisms for the long-term maintenance of antibody levels in the serum. This constitutes a major source of long-term antibody production after infection. It is likely that this long-term memory B cell-based protection mechanism is responsible for the fact that the Influenza pandemic came to an end with the acquisition of mass immunity through infection and remained subdued for some time afterwards.[12]

Memory B cells generated after Smallpox vaccination were demonstrated to be detectable by the same mechanism, even 40–50 years after immunisation.[12] Smallpox was eradicated in the 1970s. Smallpox-specific memory B cells generated at that time were maintained for more than 30 years without re-exposure to the pathogen. In addition, the Smallpox virus has not got a non-human host. When a virus has a non-human host, even if everyone in the world were vaccinated and the virus was eradicated from the human population, it would still be transmitted from animals that carried the virus as more and more immuno-compromised generations develop. With the exception of smallpox, measles and polio are the only infectious diseases that are considered to have been eradicated by vaccines. In Japan, both viruses have been established as being in a state of elimination without any outbreaks. However, there are still regions of the world where this virus is endemic, and there is concern that if vaccination is stopped, people could be infected with the smallpox virus from abroad. The disease could then easily spread.

1.4 What Has Happened in the Case of the New Coronavirus Pandemic?

Advances in research on the causes and course of infection and disease, along with the creation of treatments, innovative vaccines, and revolutionary improvements in testing, and in surveillance systems, have greatly improved the response to the threat of viral infections and its consequences.[13]

However, it was not possible to halt the pandemic. This was despite the very best efforts to protect lives by applying the highest level of science and technology. It must, nevertheless, be noted that these endeavours marked a milestone in the history of the fight against pandemics.

1.4.1 Strategies and actions to put an end to the New Coronavirus pandemic

A consensus view was announced in October 2020 by 386 representatives from various fields, including researchers, clinicians, and policy advisors representing 112 countries and regions, with the goal of ending the New Coronaviruses. This was the "Multilateral Consensus to End COVID", which was based on the Delphi method,[14] effectively summing up the opinions provided by representatives of various scientific fields. With the intention of reaching a collective agreement, each country expressed its views on the vaccination strategy it was going to use. Vaccines were indeed effective, but they were unable to bring an end to SARS-CoV-2 infections, which is still a public health threat.[15]

Instead of vaccine-dominated strategies, a Vaccine-Plus strategy was encouraged. This is an approach that combines infection-control strategies, medical care, and financial support, along with vaccination. The main rationale for Vaccine-Plus is the recognition that, regardless of the level of vaccination in each country, infection rates tend to increase when governments discontinue public health measures. These measures include lockdowns and behavioural controls, as well as basic infection preventive strategies. This Vaccine-Plus approach is based on the idea that combining vaccination with additional infection control strategies, medical care, and financial support will help to reduce the spread of disease and minimise the impact of pandemics.

Each country implemented a variety of policies to control the outbreak of New Coronaviruses, depending on their particular context. According to a statistical analysis of the effectiveness of policies[16] implemented in 79 countries and regions, the most effective policies for reduction in effective reproduction number (R) (a measure used in epidemiology to estimate the average number of new infections caused by each infected individual in a population) were the (1) prohibition of small gatherings (resulting in a 20% reduction), the (2) closure of businesses and schools, (3) border controls to restrict entry from foreign countries, (4) increased use of personal protective equipment such as masks, and (5) complete lockdown in certain countries (resulting in a 10% reduction).

The individual effects of the different policies were judged to be low, ranging, as shown, from a 20% reduction in (1) to a 10% reduction in (5).

The other analysis in 41 countries showed the reduction in R. The analysis revealed that the lockdown order was highly effective, reducing R by 51–55%, school closures by 38%, and small gatherings by 42%. In another 11 countries, the lockdown order was effective in reducing R by

81%, while school closures and the banning of public events and gatherings were largely ineffective. It was found that no single counter measure was able to reduce R to less than 1. Therefore, it is assumed that multiple counter measures are effective in reducing the number of infected people when they all work together.[16]

These analyses and the evidence to date have led to consensus at the meeting of "Multilateral Consensus to End COVID". *The consensus agreed that the highest risk of indoor transmission of New Coronaviruses is from airborne transmission by aerosols containing the virus, in poorly ventilated spaces* [15].

The following unifying, collective statement was announced:

(1) The primary cause of infection is the inhalation of aerosols containing viruses.
(2) Governments need to regulate and encourage the introduction of preventive structural measures such as ventilation and air filtration systems.
(3) The prevention of New Coronaviruses in workplaces, educational institutions, and commercial centres should be given the highest priority.

Many countries have considered and have strictly carried out these strategies in the wake of the devastation caused by the New Coronavirus Pandemic.[17]

For example,

- Belgium: The mandatory installation of CO_2 monitors and ventilation in commercial facilities and workplaces such as gyms and bars.
- USA: The US government established the Clean Air in Buildings Challenge in March 2022 to encourage owners and administrators of buildings to improve ventilation for better indoor air quality. In December of the same year, the White House issued a statement calling for fresh air requirements in approximately 1,500 federal buildings across the country. In the same December, the American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) announced that it would develop a ventilation standard (CO_2 concentration standard) by July 2023 that takes into account the risk of infection.
- UK: In July 2022, a leading government-commissioned engineering association issued a statement concerning the control of fresh air. Its implementation was intended to keep buildings safe for a lifetime.

- Japan: In 1970, ventilation to maintain indoor CO_2 concentrations below 1,000 ppm was mandated by the building code. Building administrators were obliged to inspect the air quality in the building every two months, report to the government, and then carry out improvements if the air quality had not met this standard. However, the 2020 report documented that approximately 30% of buildings inspected in 2017 exceeded CO_2 concentration standards.

The common problem in all countries is that there is no integrated structure to follow up and take responsibility for the implementation and management of ventilation. Even when laws are enacted and promoted, they are not always carried out. This makes it impossible to solve either ventilation deficiencies or achieve the original objectives.[17]

The New Coronavirus pandemic has raised the profile of the significance of the low risk of infection and the importance of healthy indoor air. It has also encouraged countries to promote and continue to improve indoor ventilation and other aspects of their indoor air quality.[17]

1.5 Can the New Coronavirus Pandemic Be Ended?

In the history of infectious diseases and related science and technology, our struggle with our fight against pandemics has been a battle against the pathogens that cause infections. In contrast to previous pandemics, we had, in our fight against the New Coronavirus, the most powerful weapons, including vaccines, drugs, advanced medical technology, testing, tracking, and surveillance technology.

But even with these weapons, the pandemic was not stopped. Effective ways to do this have yet to be found. In many countries, the response to the social stagnation caused by such a lengthy pandemic, priority may often be given to economic activity, and behavioural restrictions may well be relaxed or lifted.

Urbanisation, overcrowding, and the rapid mobility of people have accelerated in recent years. The risk of the emergence of quickly spreading highly infectious and virulent viruses is increasing.

Strategies to combat the virus have been the primary focus of the New Coronavirus pandemic. We are surrounded by mantras such as "beat the virus", "fight the virus", "living with Corona" etc.

These phrases all refer to strategies to combat the virus and specifically, are strategies being used *after* the virus has invaded the body. Therefore, the expression "living with the coronavirus", simply means that we are living with the virus while already infected by the virus.

Because all viruses, including the coronavirus, need a host to replicate, if there is no host, it is impossible for them to survive. For this reason, the "with corona" strategy, has led to repeated waves of spread. The fight to end the pandemic continued without knowing when it would end. This situation made it impossible to get back to life before the pandemic. In order to end this battle, it is necessary to break out of the limits of the "living with corona" strategy, which is simply a coexistence with the virus. We need to shift to a new non-coexistence strategy.

It is important to understand that viruses cannot multiply outside of a host cell. It becomes active only after it finds the susceptible cells to infect within the body. Once the virus has entered the body and infected cells, it multiplies at a rapid rate. As long as coronaviruses are not allowed to enter the body, that is to say, as long as they are not transmitted, the number of coronaviruses will not increase, and for that reason, the number of people who become infected will not increase.

What can be done to avoid infection?

It is entirely possible to avoid infection using today's science and technology. It can be done if we all understand, share, and implement an air ventilation approach which will stop the virus from entering the body.

2. Practices on How to Avoid Being Infected with SARS-CoV-2

To understand the way to avoid infection, we must start by getting to know how the New Coronaviruses (SARS-CoV-2) are transmitted. In other words, we must know the routes the coronas use to invade our bodies. Once we know the corona routes of infection entry, we should be able to block all possible route of entry.

It can be said, with justification, that the New Coronavirus pandemic was the first case in history in which the route of infection was properly understood. Even for influenza, people are still disregarding the aerosol route of infection, and are concentrating only on the droplet route. In fact, all respiratory infections are transmitted by the same common route. This is the same route for influenza as for the New Coronavirus. This can be well understood if we understand the aerosol routes and the droplet routes produced by breathing.

2.1 Aerosols and Droplets

The New Coronavirus infection was named SARS-CoV-2 because it is related to the corona viruses (SARS-CoV-1) that caused severe acute respiratory syndrome (SARS) in 2002–2004. The route of infection is related to respiration, in other words, breathing in and breathing out. We cannot live without breathing. When we breathe, we inhale oxygen (O_2) and exhale carbon dioxide (CO_2). CO_2 is exhaled, along with aerosols and droplets formed by exhalation[1,2] (Figure 2.1). *Aerosols and droplets behave completely differently after being exhaled. It is important to recognise the difference in their behaviour.*

2.1.1 Aerosols

Aerosols exhaled during breathing are generated by the airflow of exhaled air from the layer of liquid that covers the respiratory epithelial cells (respiratory tract lining fluid or RTLF). [1] It is similar to generating a mist of water droplets when a strong wind blows over the surface of a lake. The aerosols generated are tiny, invisible droplets that are about one-hundredth the size of the tip of a toothpick (less than 5 μm in diameter).

Aerosols contain various components and foreign substances because they float in the air currents coming from the alveoli and respiratory tract RTLF. Their composition and quantity vary from person to person. Electrolytes such as potassium, calcium, chlorine, and phospholipids of the cell membrane are aerosol components common to everyone. People with illnesses or infections have disease-specific components, because of, for example, the medications they take, and infectious pathogens (bacteria, viruses), each of which is contained in the aerosols.[1, 2, 3, 4,9,11] The aerosols from COVID-19 patients contain the New Coronavirus, SARS-CoV-2. It is known that respiratory infection patients suffering from influenza, colds, measles, smallpox, pneumonia, and tuberculosis have their respective pathogenic viruses or bacteria contained in the aerosols.[3, 4, 10]

The human respiratory volume (ventilation volume) is 6 ml x (body weight kg) per breath, at rest. For an average adult, this comes to approximately 0.5 litres (400–530 ml) per breath[5]. At rest, the respiratory rate is about 8 breaths per minute, so the respiratory volume per minute is about 0.5 (litre/breath) x 8 (breaths/min) = 4 litres/min. During light exercise, the respiratory volume is about 12 litres per minute, and it increases further during activities such as talking, singing, or exercising.

Accurately measuring the amount of a through respiration is technically challenging, but it is estimated to be 44[5] to 98[1] particles per litre. Therefore, at rest, approximately 44–98 (aerosol particles/litter) x 4 litres/min = 176–392 aerosols are emitted per minute. For example, when an adult is sleeping, he/she emits 10,560–23,520 aerosols per hour, and during 8 hours of sleep, he/she emits 84,480–188,160 aerosols.

During conversation, it has been reported that approximately 88[5] particles per minute are emitted. When singing or exercising, even more aerosols are emitted[5].

2.1.2 Re-breathing and circulation of indoor aerosols

Aerosols generated through respiration can be re-breathed and shared among others sharing the same indoor space. As shown in Figure 2.1, aerosols generated in the respiratory tract can have different characteristics for each individual. The aerosols from infected individuals can contain viruses or bacteria.

In an enclosed indoor environment, aerosols generated by the breathing of everyone present in the room float and mix in the air. Over time, the total number of aerosols increases. People in the room breathe in the mixed