

Syndemic of Coronavirus Disease and Metabolic Diseases: A Global Perspective and Call for Action

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Ravages of a 16 trillion-dollar killer virus (SARS-CoV2) worldwide, has caused an unprecedented healthcare crisis [1]. According to the global health experts, the coronavirus disease (COVID-19) pandemic has demonstrated the critical need, to reimagine and repair the broken systems of global health. Global experts in public health write in the Journal of Global Public Health, “We are living in a historic moment, a crisis brought on partially by a virus, SARS-CoV2, and partially by the defunding of basic public health systems in the context of longstanding global power differentials [2]”. The health experts conclude, “This historic pandemic offers an opportunity for a pivotal shift in global health agendas. For our health and the health of the world, we must usher in a new paradigm of global health guided by real collaboration, solidarity, and equity. In this invited article, I would like to take these thoughts a little further to explain how a syndemic of a novel infectious disease (COVID-19) has cleverly taken advantage of an existing pandemic of metabolic diseases and caused an unprecedented health care crisis. Furthermore, I will try to explain how the modern medicine approaches have failed to reduce, reverse, or prevent chronic metabolic diseases. Finally, I will advocate the need for an integrated approach to develop sustainable global public health policies. In a short overview like this, it is not possible to cover all aspects of this public health problem. Readers are urged to refer to comprehensive reviews on this topic.

We and other experts have described the increasing incidence of metabolic diseases such as hypertension, excess weight, obesity, type-2 diabetes (T2D) and vascular diseases as pandemic, epidemic, or tsunami in our earlier publications [3-9]. Globally, an estimated 26% of the World’s population (972 million) has hypertension. The prevalence of obesity currently is 40% among young adults aged 20 - 40 years, 45% among adults aged 40 - 60 years and 43% among adults aged 60 and older. A new study from the Imperial College, London, reports a tenfold increase in childhood adult obesity in four decades, from 11 million in 1975 to 124 million in 2016. T2D has become the biggest epidemic of this century worldwide. China and India lead the world, in terms of number of diabetic individuals. It is interesting to note that there are more prediabetics in the world than diabetics. In the USA the estimated number of diabetics is 30 million. Whereas, according to the US Center for Disease Control (CDC) and prevention, there are more than 100 million prediabetics. Diabetic populations in China and India are close to 116 million and 80 million respectively. Worldwide prevalence of prediabetes is estimated at 463 million. Vascular diseases are the most common noncommunicable diseases globally, responsible for 18 million deaths in 2017, of which more than three quarters (43%), were in low-income and 42% were in middle-income countries [9-14].

Just over a decade ago, the late Nobel laureate Joshua Lederberg wrote, that “the future of humanity and microbes likely will unfold as episodes of a suspense thriller, that could be titled ‘Our Wits and Their Genes’ [15]”. He also predicted that, “the process of gene reassortment in viruses, goes on relentlessly, and is sure to regenerate human-lethal variants [16]”. Coronaviruses such as SARS-CoV2 are relatively stable because they have a proofreading mechanism, to delete unwanted mutations as they replicate. In general experts agree,

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that natural selection allows to make mutations that help the virus spread more effectively. Studies done in UK with the analysis of over 23,000 genomes, found evidence that the UK variant (B.117/501Y.VI) of the virus outdistances its competitors in terms of rate of infection. Now the UK researchers are concerned about the Indian variant (B.1.617.2) in terms of its transmissibility and severity. As of this writing COVID-19 has spread to all the countries and globally has infected more than 161 million individuals and has caused 1.4 million deaths. In the USA, it has infected over 33 million and has caused 585 thousand deaths. In India, the current epicenter of COVID-19, more than 24 million are COVID positive and over 266 thousands have succumbed to this disease.

Coronaviruses have positive-sense RNA genomes, consisting of six conserved proteins. The conserved proteins are the polyproteins pp1a and pp1b, that encompass multiple protein domains involved in various aspects of coronavirus genome replication. Size of this virus is between 60 nanometers (nm) to a maximum of 140 nm. Respiratory droplets are typically 5 - 10 microns, and each droplet may contain 250 virions, which means just normal talking can generate more than 750,000 virions. The genome of the virus is around 29.8 kilobase, containing six open reading frames. The main mode of transmission is through respiratory particles. Spike (S) proteins of SARS-CoV2 seem to have 10-to-20-fold higher affinity to the human angiotensin enzyme (ACE2) receptor than that of SARS-CoV. The high affinity of S proteins to the ACE2 receptor, the ubiquitous distribution of this enzyme in various tissues, and the additional advantages offered by the transfection facilitators Furin and Neutropilin-1, likely contribute to the rapid spreading of this virus. Since this enzyme is highly expressed on a variety of cells, including vascular endothelial cells and adipose tissues, individuals with compromised function of these tissues drive greater infection and severity in patients with underlying medical conditions [17,18]. According to a Center for Disease Control (CDC) report (August 30, 2020), 94% of the COVID-related deaths were associated with underlying health conditions.

The most prevalent clinical symptom for COVID-19 is fever (84.49%), cough (56.39%), fatigue (33.65%), dyspnea (22.34%), sputum production (22.34%), and myalgia (16.26%). Other symptoms reported include, shortness of breath, diarrhea, headache, chest pain, vomiting, sore throat, poor appetite, loss of smell and taste, and chills. The most prevalent comorbidity reported is hypertension (20%), cardiovascular disease (11.9%) and diabetes (9.8%). Other less know comorbidities include, excess weight, obesity, chronic kidney disease, chronic liver disease, chronic pulmonary disease and cerebrovascular disease. Of the total hospitalized COVID-19 patient population in the USA, 89% had at least one pre-existing chronic condition according to the CDC, USA. Approximately 50% reported hypertension and obesity, a third reported diabetes, and a third had CVD. In the early studies conducted in China, the most distinctive comorbidities were cerebrovascular disease (22%) and diabetes (22%). In a second study, again hypertension was the leading comorbidity (23.7%) followed by diabetes (16.2%). In a third study reported from China, 30% had hypertension and 12% had diabetes [18]. In the USA, excess weight and obesity are major comorbidities for the severity of COVID-19. Data from 6916 patient records that researchers from Kaiser Permanente analyzed, compared to normal body mass index (BMI) of 18 - 24 Kg/m², the risk of death more than doubled for patients with a BMI of 40 - 44 Kg/m² and nearly doubled again, for those with a BMI of 45 kg/m² or more. Experts estimate that 1.7 billion people of the global population have at least one underlying condition, that puts them at risk for COVID-19.

Unprecedented coronavirus disease is a pandemic over another pandemic, 'metabolic diseases', which have provided a large population of 'at risk' individuals, for this killer virus. A recent Comment (September 26, 2020), published in the journal Lancet, says that COVID-19 is not a pandemic, it is a syndemic. Both these pandemics were anticipated by the public health experts. There were considerable warnings about the need for a better global healthcare infrastructure, a better global leadership. A report by the Lancet Commission on the Public Policy and Health examined the recent health policies in the USA and concluded that, "Disdain for science and cuts to global health programmes and public health agencies have impeded the responses to the COVID-19 pandemic, causing tens of thousands of unnecessary deaths [19]. In a scathing editorial, top scientific journal (Lancet May 9th, 2021) criticized the mishandling of the second surge of COVID-19 in India [20]. Despite the warnings about the risks of super spreader events, the government in both the USA (previous administration) and India, allowed people to gather at various super spreader events. Populist leaders around the world are a liability.

According to some experts their optimistic bias, complacency, ambiguity, and ignorance of science has undermined the COVID-19 crisis management. Furthermore, in this unprecedented pandemic, politicians interfered in public health science and its implementation [21]. Scientific professional platforms like Center for Disease Control and Prevention, Food and Drug Administration, National Institute of Health and the World Health Organization have lost their credibility.

Four democratic countries, the United States, India, Brazil, and the UK are the top four countries in the world which form an 'infectious league.' The US, the oldest democracy leads the group by a wide margin: currently, it has over 33 million infected individuals with 585,651 COVID-related deaths. India has 24 million COVID positive individuals with 266,207 deaths. Brazil has 15 million COVID positive individuals with 432,628 deaths. Mr. Talmiz Ahmed in an opinion column in *The Wire* (June 29, 2020) writes, "From the US and Brazil to India and the UK, the very qualities that catapult populist leaders to power are those that make them dismal failures at handling a serious national health emergency". Both the Coronavirus disease and metabolic diseases are global public health problems. Considerable warnings were given by the public health experts on how to handle global public health emergencies. However, just warning, or publishing statistics on these epidemics will not solve the issues. Even though member countries of the United Nations signed an agreement to lower the incidence of Type-2 diabetes by 2030, very little progress has been made in reducing reversing or preventing metabolic diseases. Just consider the case of a single disease, diabetes for instance. According to the International Diabetes Federation, the global shift in the burden of diseases has not been reflected in the policy priorities of donor countries and global health care organizations.

Countries grappling with infectious diseases, now face a double burden of diseases, coronavirus disease and metabolic diseases. In the absence of a cure for coronavirus disease, we are left with only two choices. Vaccinate every individual worldwide or implement strict public health best practices such as use of face masks, hand washing, social distancing, contact tracing and quarantine of the COVID positive individuals. Except in a handful of countries, availability of vaccines is limited. COVAX is one of the major pillars of the Access to COVID-19 Tools (ACT) Accelerator, which was launched in April by the World Health Organization, the European Commission, and France; coordinated by Gavi, the Vaccine Alliance, the Coalition for Epidemic Preparedness Innovations (CEPI), and the WHO. COVAX will support research, development, and manufacturing of a wide range of COVID-19 vaccine candidates. For low-income and resource-poor countries, COVAX is a lifeline and the only viable way to get access to COVID-19 vaccines. According to the director of WHO, COVAX needs USD 45 billion to develop vaccines sufficient to vaccinate eligible individuals around the globe.

Another alternative is to achieve herd immunity for the virus. According to the researchers at the Usher Institute of Population Health Sciences and Information, Edinburgh, herd immunity by infection is not an option [21]. They conclude, "Achieving herd immunity naturally through infection will be very costly in terms of mortality and morbidity". They discuss a case in point, the experience in Manaus, the capital of Amazonas state in Brazil, where mortality rates of a largely unmitigated outbreak with an estimated infection of 76% of the population, herd immunity was not achieved, providing a cautionary example of lack of herd immunity with even such high COVID positive cases. How about the vaccination providing total immunity? The Indian Ocean nation, Seychelles is the most vaccinated nation on earth as of this writing. Yet according to the ministry of health, a third of people who tested COVID positive in the week of May 8th, 2021, had been fully vaccinated. Most vaccinated people have received China's Sinopharm vaccine (WHO approved), as well as AstraZeneca. This situation also reminds us that no coronavirus vaccine currently in use has been proven to be 100% effective at preventing COVID-19 infection.

World Health Organization is reclassifying the highly contagious triple mutant COVID variant from India (B.1. 617) as a potential global health risk. As we have discussed already, the metabolic diseases have reached an epidemic proportion worldwide. Because of underlying metabolic diseases more than a billion people globally are 'at risk' for COVID-19. Therefore, both metabolic diseases as well as coronavirus diseases are global health threats and cause unprecedented economic problems if unmitigated. Global healthcare emergencies require a consorted effort by the world community. The days of propagating isolationism are over. We need a united front to address and plan

for the global health emergencies. An international analysis of lockdown and virus suppression indicated that countries which imposed the strictest form of lockdown resulted in significant reduction in growth and new confirmed cases [22]. Implementing any lockdown is controversial as it will affect the wellbeing and economic welfare of the country. The cultural issues also have challenged the UK and the USA where it is now evident that face masks do have a positive use against the spread of infection. Despite this observation, there is considerable resistance in large group of population against the use of face masks in the USA. A lack of clear ownership and leadership internationally and nationally have partially affected the achievement of appropriate preventive strategies for global public health problems.

The COVID pandemic has forced the Member States at the United Nations General Assembly to adopt unprecedented working methods as world leaders grappled with the far-reaching consequences of the global health crisis. The main session focused on the theme “The future of what we want, the United Nations we need: reaffirming our collective commitment to multilateralism-confronting COVID-19 through effective multilateral action”. We remind the world leaders their earlier pledge to reduce or reverse the global burden of metabolic diseases. This reminder is a call for action since the individuals with underlying metabolic disease are at risk for coronavirus disease severity. “We have come far in 75 years, but much more remains to be done,” stated the Declaration, which emphasized that implementing the 2030 Agenda for Sustainable Development-adopted at the Assembly’s seventeenth sessions- is a necessity for the survival of the humanity. The Declaration stated: “We have the tools and now we need to use them. Urgent efforts are required. Therefore, we are here not to celebrate. We are here to take action”.

Metabolic diseases such as hypertension, excess weight, obesity, vascular dysfunction (endothelial dysfunction) and vascular diseases have increased in incidence and prevalence to epidemic proportions worldwide. Coronavirus disease is known to be much more severe in individuals with such underlying metabolic diseases. One in five individuals globally are at risk for COVID-19 because of underlying health conditions. There is an immediate need to mitigate the COVID-19 pandemic worldwide for the survival of humanity. Global efforts should concentrate on providing the urgent care needed to mitigate COVID-19 worldwide. Globalization has led to tremendous interdependence and as such no country can ignore the present needs for collective preventive efforts. No country has reduced or reversed the increase in the incidence of metabolic diseases. Considering the economic burden of uncontrolled metabolic diseases, the global healthcare providers and other professional organizations should make serious efforts to reduce or reverse the incidence of metabolic diseases.

The Director of World Health Organization Dr Adhanom Ghebreyesus lamented recently, that vaccine supply remains a key challenge and that saving lives and livelihoods with a combination of public health measures and vaccination-not one or the other- is the only way out of this pandemic. As far as the vaccine goes, only 0.3 percent of the vaccine doses administered globally have been given in the 29 poorest countries. Even in an advanced country like the USA only 38% (May 18, 2021) of people are fully vaccinated. In the largest democratic country, India, less than 15% of the eligible population is vaccinated. Two countries with great surges of Coronavirus India and Brazil have not been able to vaccinate their population fast enough to flatten the curve. European Union leaders told a global summit: “Vaccination is a universal human right”. Globally about 720 million people (9% of the population) have been vaccinated and there are more than seven billion people still to be vaccinated. Even vaccination is not a permanent solution to this growing pandemic. Novel interventions are being discovered as we are writing this overview. Nanobodies have been discovered which are small, stable, and simple to produce, and hold promise as therapeutic proteins to be used in novel interventions for COVID-19 [23,24].

In the absence of a global health policy, it is a struggle between the haves and have nots. In the absence of a cure for COVID and unavailability of vaccines, it is left to the individuals and health care workers to develop best health practices, that can keep the population free of new infection. If the virus cannot find you, then you cannot get infected. The simple sure way of protecting from the virus is to avoid contact with sick people, follow social distancing guidelines, avoid crowded locations, use face masks, wash your hand with soap. At the population level, limited lockdown, contact tracing, quarantine of the COVID positive individuals has worked the best. Taking a few precautions now seems to be the best defense in preventing and avoiding illness from this novel, killer coronavirus.

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