Opinion Paper

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Zealous clout of COVID-19: analytical research at sixes and sevens

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Abstract: This New Year's wake-up call warned us of Democles' sword in the form of COVID-19, an epidemic turned pandemic. Seeming to reach a novel and awful landmark every day, governments across globe are fighting on toes to contain its spread. The pandemic is accelerating and information is being updated and changing by the hour. Till date shattering causalities across globe have been reported to World Health Organization. Nevertheless, the world is responding to this novel enemy with urgency and purpose. The challenge is great, but the response has been massive. Record characterisation and multiple sequences of this novel pathogen are being shared on global platform leading to a lot of diagnostics to get developed. Currently no treatment is effective against COVID-19 and there is a desperate need for international solidarity for valuable therapeutics. Present article briefs some milestones achieved by the killer virus thereby posing a challenge to medical science.

Keywords: alarming situation; COVID-19; effective therapeutics; global platform; medical science; shattering causalities.

Introduction

Disease and illnesses have plagued humanity since the earliest times, our mortal flaw. A disease spreading actively over a wide geographic area and affecting an exceptionally high proportion of the population is epidemic. However, when the epidemic relates to geographic spread and affects a whole country or the entire world, it becomes pandemic. Widespread trade created new opportunities for human and animal interactions that sped up such epidemics. The more civilized humans became – with larger cities, exotic trade routes, increased contact with different populations and ecosystems – the more likely pandemics would occur. Throughout history, there have been a number of such incidents. For example, the last recent pandemics we can mention include; Plague (1720), Cholera outbreak (1820) and the most recent one was Spanish flu (1920). The deadly bubonic plague started in Marseille and was later called 'The Great Plague of Marseille'. The number of deaths estimated was 100,000. In 1820, the first pandemic occurred, somewhere in Asia in the form of cholera. Among the affected countries, lists Thailand, Indonesia and the Philippines. This pandemic also killed approximately the same number of people. Roughly 100,000 officially registered deaths. Outbreak of this pandemic has been reasoned to be the consumption of water from lakes infested with the concerned killer bacterium. In 1920, one of the most unremitting pandemics occurred. This was the Spanish flu known to infect about half a billion people and killed ca. 100 million. Being so devastating, The Spanish flu holds the official record for the most life threatening pandemic officially recorded in history (Rahman 2020). It is now 2020. Exactly at the 100th anniversary of the Spanish Influenza, humanity is facing a new potential pandemic in the form of 'Coronavirus'.

The outbreak of coronavirus started in mid-December 2019 in Wuhan, a sub-provincial city and the sprawling capital of China's Hubei region. Nobody knew about it until a couple of months ago, when authorities

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were trying to understand the actual cause behind a cluster of mysterious pneumonia cases in China's Wuhan city. Initially, the Chinese government was beating about the bush and reluctant to make any official statement on the disease. Tried to keep their cards closed, the situation, however, worsened rapidly and in no time it fanned across the globe. At present the situation has worsened to such an extent that the human race is tangled in a battle against a creature which is nearly $1/5 \times 10^{-6}$ th part of it. The present article is, therefore, an endeavour to consolidate the milestones achieved by the deadly virus till date and how in due course of time it influenced humanity across globe. It is pertinent to mention here that the author has framed this article by reviewing the published literature on COVID-19 based on the information available at a particular time. At the same moment, utmost care has been taken to juggle multiple tasks, from digging up and evaluating the pertinent material to synthesising information from various sources including the web based data base, electronic and print media as well, from critical thinking to paraphrasing, appraise, and citation skills.

Humanity's newest foe: situation in numbers

Amid corona pandemic, impact of COVID-19 has darkened all our lives. Off roading from Wuhan, the deadly virus shortly flew to other countries. It took 67 days from the first reported case to reach the first 100,000 cases, 11 days for the second 100,000 cases and just four days for the third 100,000 cases. By June 15, the number of COVID-19 cases as reported by World Health Organization (WHO) surpassed 7,800,000 globally, and more than 430,000 people have lost their lives. Figure 1 illustrates the epidemic curve of COVID-19 cases worldwide as of June 15, 2020 (last update by WHO 2020).

The virus is drastically unforgiving and has overwhelmed health systems, including the ones which are among the best. As novel corona spreads across the globe, each country hopes that it has the ability to slow its growth in its own country. As of today, European Region falls in last place with regard to limiting COVID-19 growth according to the number of confirmed cases. As per the COVID-19 situation report-147 (latest update) by WHO, the number of positive cases in European Region grew at a faster rate than any other region in the world. Figure 2 illustrates how these numbers are skewed among six regions and the number of casualties in just a 24-h period.

Coronavirus-hit globe: lost halcyon days

COVID-19 virus has an ultimate potential to prematurely end millions of lives. In just a very short time, a virus initially undermined by politicians has pulverized the entire globe to a halt and made it to hang by a thread. A broader public debate on the rationalization of various bizarre measures and the power make ups they uphold

Figure 1: Epidemic curve of confirmed COVID-19, by date of report and WHO region, as of June 15, 2020.

Figure 2: COVID-19 cases: Situation in numbers as of June 15, 2020.

is hampered by the authorities' recommendation to stay at home and to practice 'social distancing' now turned to be 'personal distancing'. Travel restrictions and border closings effectively downplay transnational debates and impair the solidarity across globe. In this context all countries across globe put their fingers in the pie and declared 'people's war' against the coronavirus epidemic. This has made innumerable lives under varying degrees of lockdowns with only essential services to remain operational. Consequently, Covid-19 pandemic has forced retail and food outlets to remain closed to avoid the spread of the disease and comply with the lockdown measures.

The improvised redistribution of public means to the benefit of already privileged classes (corporations, skilled labour, financial industry etc.) can barely be questioned. Those who are badly affected by the corona crisis (homeless persons, low-income single parents, day labourers, and migrants) are prevented from eloquencing their wobbly situation. More importantly, the flinching space for public debates makes it quite difficult to problematize the paucity in the two civic healthcare systems resulting from the 'retreat of the state' (Strange 1996) under the assertion of ongoing neo-liberalism. While addressing potentially disastrous consequences of the pandemic throughout the world, an international vision is virtually lacking and barred by augmenting dread-fueled 'identity politics' (Hobsbawm 1996) in mechanized countries. Apparently, when the need for solidarity is most dire, it is in short supply.

The present article neither questions on the aptness of public health measures, nor rebuffs all economic interventions. Nevertheless, it is to be feared that public means will once again be mustered for personal expansion. Need of the hour is, therefore, to avoid coronization of the present predicament. The perception of an emergency must not be battered to underpin those communal, fiscal as well as political inequalities which are at the origin of the existing emergency.

Portraying possible origin

An unprecedented amount of research has been focused solely on understanding the deadly novel coronavirus. Amid corona pandemic four crucial and burning questions are occupying virologists that have evaded

any definitive answers. Where did the virus come from? What makes the new virus so active and vibrant for infecting people? How does it reproduce so quickly once it makes its entry inside a human cell? And why does not the virus cause symptoms straight away, allowing it to spread undetected? However, tracking the precise journey of a peripatetic virus is very tricky as nature seldom follows linear routes. Despite such cordons, researchers have been undeterred in their hunt, piecing together a travel map of coronaviruses. While scientists have been able to figure out most of the intimate details of SARS-CoV-2, corona pandemic has divided opinions among researchers and scientists across globe which has prevented them to arrive at unequivocal conclusion(s). Research going on at pace explains two possible ways how COVID-19 virus might have originated. Few scientists including Dr. Kristian Andersen, an associate professor of immunology and microbiology at the Scripps Research Institute in La Jolla, CA, and his colleagues believe virus to have evolved first, became pathogenic in bats, and then leaped to humans (Andersen et al. 2020). This concept of origin is congruent with that of other coronaviruses, including SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) (Sethy and Behera 2020) since SARS-CoV-2 shares much similarity with bat coronavirus (Figure 3). This hypothesis also explains rapid spread of the virus and suggests two prominent features of SARS-CoV-2's spike proteins having made it possible to inflict havoc before entering humans. This, in turn, supports the higher probability of its future outbreaks as the pathogenic strain of the virus would still be circulating in animals and could jump back into humans at any point.

Refuting investigations by different scientists have put the theory of SARS-CoV-2 origin from bats to rest and related ideas to bed. Virus is believed to be non-pathogenic in animals and must have dived into humans and evolved into a disease-causing strain there. Finally, this concept is in line with the theory that places pangolins, the illegally trafficked mammals (Figure 3) at the start point of the outbreak followed by bats since the spike proteins of some coronaviruses from pangolins share a similarity in RBD structure with that of SARS-CoV-2.

Figure 3: Potential transmission route of SARS-CoV2 (formerly 2019-nCoV).

Thus, novel virus has made scientists across globe to talk in circumlocution and it does not seem to be conclusive by any means. Consequently, it has become impractical to say which scenario is more likely to be operative at this point of time. However, as the situation soars worldwide, it has become central to trace the origin of the infection and find out the ways to prevent such infections from recurring.

Zoonotic aspects

Zoonotic diseases are known to spread from animals to humans. Though a rare phenomenon, humans can also act as vectors infecting domestic animals. Before SARS-CoV-2 turned pandemic, many incidents had already been popping up on farms. In late 2016, for example, more than 25,000 pigs died across four farms in Guangdong province of China. These infected pigs were symptomatic for the swine acute diarrhoea syndrome (SADS) causing severe vomiting and diarrhoea. An indepth investigation of the causal virus revealed its genomic sequence to be almost identical to the coronavirus found in horseshoe bats in a nearby cave. It was a familiar crossover from bats to animals, with pigs as victims that time. A disquieting part is that pigs and humans have comparable immune systems, making humans also extremely vulnerable to SADS.

In SARS-CoV-2, ACE2 (Angiotensin-Converting Enzyme 2) is a universal receptor common among birds, reptiles, amphibians, mammals, and fish. At present, species most vulnerable to the SARS-CoV-2 and ACE2 interlock are humans, a few primates, as well as cats, which helps explicate why a few domestic cats in the United States and Europe have come down with mild COVID-19 symptoms. Another reason why animals, for example, dogs can become prone and get sick with the deadly virus is less to do with their ACE2 receptors but more with the frequency of their exposure to infected humans. Similarly, researchers at Indian Council of Medical Research (ICMR) found a bat coronavirus (BtCoV) in two bat species from Kerala, Himachal Pradesh, Puducherry and Tamil Nadu bearing no relation with SARS-CoV-2 responsible for the Covid-19 pandemic. However, fortuitous transmission thereof to humans and other animals may result in severe respiratory complication syndrome, and other enteric, hepatic or neurologic diseases of variable severity. It is still not comprehended why only certain coronaviruses can infect people. It is, therefore, urged to have a proactive surveillance of zoonotic infections in bats. According to ICMR, detection and identification of such viruses from bats urges cross-sectional antibody surveys (human and domestic animals) in the localities where the viruses are suspected to be detected. Development projects in countries like China, India, Brazil, and Nigeria, have already begun with an approach beyond wildlife borderlands. This hostile edge with forested areas can result in numerous novel zoonotic diseases. At the same time, consumption of wild game due to bottomless cultural beliefs isn't going to perish but can only be phased out by concerted efforts. The international infringement of nature calls for the guidelines for the outbreak of future epidemics unless a rigorous multi-directional approach is adopted sooner than later.

COVID-19 prophylactic: to date there is none

With an unknown travel history and a budding potential to prematurely end millions of lives COVID-19 has pounded the entire globe to a standstill and made itself to remain unresolved. When the entire world is trying to combat this pandemic, labs round the world are working around the clock by leaps and bounds in a bid to eradicate their enemy. Despite several ongoing clinical trials of both western and traditional medicines (Chu et al. 2020; Chung et al. 2020; Corman et al. 2020; Huang et al. 2020; Li et al. 2020; Wang et al. 2020; Zhang et al. 2020), to date there is no effective therapeutics to prevent or treat it. Critical brown research is, therefore, desperately required to help design treatment to stop it. Offering the first shot to test the potential vaccine for COVID-19 on March 16 by United States spurred a cascade of worldwide hunt for effective antidote. More than 100 research institutes throughout the world are racing to create a vaccine against virus. While many of them have claimed for successful vaccine preparation (Table 1), some have declared to initiate human trials. As per a report in The Science Times on 5-May-2020, 'Italian scientists claim to have developed World's first COVID-19

vaccine'. Prepared by the doctors at Rome's Lazzaro Spallanani National Institute for Infectious Disease, this antidote has successfully generated antibodies in mice and the vaccine is expected to neutralize the coronavirus in human cells too. Nevertheless, it is yet to undergo human trials. Meanwhile, an Indian news channel India TV on March 22, 2020 flashed a news about President of Super Power America Mr. Trump recently claiming for a "miracle" to happen since scientists at Oxford and Johnson & Johnson Multinational Corporation Labs are working on more than 95 vaccines with tremendous amount of progress. He asserts with confidence that very soon weapon to kill bio-weapon will be in front of the world. Just recently, a combined study from Indian Institute of Technology (IIT) Delhi's DAILAB and Japan's National Institute of Advanced Industrial Science and Technology (AIST) made the discovery that Ashwagandha (*Withania somnifera*), can prove to be the crucial medicine in fighting coronavirus and can be even used in the development of a vaccine. Withanone (Wi-N), a potential compound derived from Ashwagandha and Caffeic Acid Phenethyl Ester (CAPE), an active ingredient of Propolis, have been found to interact with Main protease (Mpro), the main SARS-CoV-2's enzyme for splitting proteins and playing a key role in mediating viral replication. Both the natural compounds have the ability to bind to the substrate-binding site of SARS-CoV-2's Mpro with efficacy and block its activity (Kumar et al. 2020). India's Ministry of AYUSH and CSIR announced a slew of measures and clinical trials aimed at studying the use of Ashwagandha, along with other Ayurvedic herbs as a preventive treatment to front line workers and infected patients in a large study which is to start soon. Other medicines under study include Guduchi (*Tinospora cordifolia*), Yasthimadhu (*Glycyrrhiza glabra*), Peepli (*Piper longum*) and another formulated drug, 'Ayush 64', and would be undergoing human trials soon.

As the world's leading group of scientists and researchers race to find an antidote to fight the killer coronavirus, which has reportedly infected millions globally, there's a pressing need for a workaround to beat the virus. Nevertheless, the fact is that till date no country, no scientist across globe could say it with confidence that they have developed the potential and effective antidote against deadly coronavirus. With the result, cataclysmic ruinations are reported to WHO on daily basis from across the world. However, the globe is responding to this killer virus with urgency and purpose. Isolation has become the way to escape coronavirus infection and tests since there is a dearth of sufficient kits or the risk of shortage in hospital beds. Nevertheless, there is an urge to understand the challenge that not only the government is facing especially in terms of a

Table 1: Clinical-phase vaccine candidates for Sars-Cov-2.

Candidate	Vaccine characteristics	Developer	Current status
mRNA-1273	Based on RNA technology with LNP-encapsulated mRNA encoding S-protein.	Moderna Therapeutics, Cambridge in collaboration with National Institute of Allergy and Infectious Diseases, America	Phase II (NCT04283461)
Ad5-nCoV	Adenovirus type 5 vector that expresses S-protein.	Cancero Biologics together with Institute of Biotechnology and Academy of Military Medical Sciences, China	Phase II (NCT04313127)
INO-4800	Based on DNA plasmid encoding S-protein delivered by electroporation.	American Biotech Company INOVIO Pharmaceuticals	Phase I (NCT04336410)
LV-SMENP-DC	Lentivirus vector that expresses synthetic minigenes based on domains of selected viral proteins.	Shenzhen Geno-Immune Medical Institute, China	Phase I/II Multicenter Trial (NCT04276896)
ChAdOx1	Based on adenovirus vaccine and manufactured using some genomic modification in ChAdOx1virus, otherwise responsible for causing cold in Chimpanzee.	Jenner Institute of Oxford University, Britain	-
Pathogen-specific aAPC	Artificial Antigen-Presenting Cell (aAPCs) modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins.	Shenzhen Geno-Immune Medical Institute, China	Phase I (NCT04299724)

critical demand for ventilators and beds in intensive care units but also researchers and scientists are undertaking via a critical demand for a potential antidote to contain the disease and eradicate the deadly virus.

Chaos in journals – do they lose standards for papers on COVID-19?

What the entire globe comes to know about COVID-19 via research is changing at a pace beyond imagination. And people from civic to politicians to media baffle the possible with the probable. Ultimately, it results in a lot of gratuitous guilt and fear. Under such conditions, one usually approaches to experts to certify things but what one should consider when the experts themselves are not aware and have a big question mark? Whatever little everyone gets to know tries to add to the information on COVID-19. With the result, within a short span literature has flooded with data on this novel virus, much of which is vague. However, the pace of legitimate scientific thought process can only go so fast. Consequently, chaos emerges in journals as they are at the brink to lose their standard for papers on novel coronavirus to help scientists share information. Corona pandemic has divided opinions for analytical research among scientists and researchers across globe. While one group of scientists advocates mutations in novel coronavirus resulting in two strains, one more dangerous than the other, other group refutes after re-examining the data. This is a clear glance towards how the original research over-interpreted the data; though original finding got instant, undeserved press. Similarly models showing rate of viral infection are currently grasping much attention, but many work at speed without incorporating the known physics, chemistry and biology of virus life cycle including transmission and replication. There is a big question, for instance, whether ibuprofen interfere with the body's natural immune response to COVID-19, or help stuff patients fight it? This went from recommendations to dejections. However, the former is based on The Lancet Paper expressing its due uncertainty. Clearly, breaking of COVID-19 from epidemic to pandemic make journalists remain under stress in order to get faster updates.

People understandably yearn for certainty and so divulging something which is yet to be worked out, or is credible but improbable, won't get as many clacks as a story that promises answers. Well that arranges a stage for bad selection process where in the populace pays attention to the most confident experts over the most competent. Those who divan things in ambiguity get misconstrue. Although the pace of data acquisition has and is being accelerated but, the ability to publicize information is one step ahead; we can share false certainty faster than we can create useful knowledge. One should abide-by this fact that there are times when we have definitive answers, but science works in a probabilistic realm.

Globe is biting off more than it can chew. Encouraging more scientific work is smart. Grasping at straws is wasted energy!

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