

# Temporal Unpredictability and Probabilistic Uncertainty Induced Anxiety in the Times of COVID-19 Pandemic

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## ABSTRACT

Human beings prefer a predictable and certain environment over an unpredictable and uncertain environment. No one predicted the coronavirus pandemic and it is not certain when the pandemic will come to an end. Pandemics not only affect the physical health but also the mental health of the public. An increase in anxiety and suicide rates has been reported during the previous pandemics and the same trend is also being observed in this current pandemic as well. Pandemics inevitably result in unpredictable and uncertain environments. Many studies have proven that unpredictability and uncertainty increase the levels of stress and anxiety in animals and humans. Coronavirus pandemic has caused many unpredictable and uncertain events resulting in increased confusion, frustration, stress and anxiety among the public. For instance, the institution of lockdowns was unpredictable and it was uncertain when the lockdowns will be unlocked. Similarly, events that unfolded around the initial touting of chloroquine and hydroxychloroquine as a possible therapeutic agent and later lack of evidence in support of these drugs resulted in extreme confusion and frustration. The uncertainty around if a vaccine for coronavirus will be developed and when it will become available for public use has also caused stress and anxiety. Current studies indicate that coronavirus is not just a respiratory virus but it also affects the kidneys, brain, heart and blood vessels. This unpredictable nature of the virus has caused further confusion and frustration. These unpredictable and uncertain events around the current pandemic might have increased the levels of stress and anxiety among the public.

**Key words:** Coronavirus, Pandemic, Unpredictability, Uncertainty, Stress, Anxiety, Suicide.

## INTRODUCTION

In his famous theory of the hierarchy of needs, Abraham Maslow proposes that a need for safety comes next to physiological needs like food, water, rest, warmth etc. for human beings.<sup>1</sup> A few examples of safety needs are personal security, financial security, emotional security, social stability, freedom from fear and most importantly health and well-being.<sup>2</sup> But Abraham Maslow also concedes that “practically everything looks less important than safety, even sometimes the physiological needs which being

satisfied, are now underestimated. A man may be characterized as living almost for safety alone”. Recent studies also claim that safety needs are even more important and fundamental than physiological needs.<sup>2,3</sup> To feel safe, people need order, certainty and control in their lives. Order is when people can predict everything in their environment and everything in their environment is certain. Human beings prefer a certain and predictable environment over an uncertain and unpredictable environment.<sup>4</sup> In a

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certain and predictable environment, people can lead a satisfied, stable, calm, competent and healthy life.<sup>5</sup> On the other hand, unpredictability and uncertainty in life cause fear, stress, anxiety and associated disorders.<sup>6</sup> Studies have shown that unpredictable and uncertain events cause responses that mimic a sustained state of distress and anxiety rather than short term fear.<sup>7</sup> Temporal unpredictability is defined as ambiguity in when an event will occur and probabilistic uncertainty is defined as ambiguity in how likely an event is to occur.<sup>8</sup> Several animal and human studies have shown that temporal unpredictability and probabilistic uncertainty causes an increase in the levels of anxiety and associated disorders.<sup>9,10</sup>

A cluster of cases with pneumonia was first reported in Wuhan city, China in the month of December 2019. The cause of this was later found to be a highly pathogenic viral infection caused by SARS-CoV-2. On 11<sup>th</sup> March 2020, the World Health Organization (WHO) declared the novel coronavirus (COVID-19) outbreak a global pandemic.<sup>11</sup> Governments and people all over the world failed to realize and accept the reality and potential consequences of COVID-19 at the initial stages of global pandemic. But as the number of infected cases and death rates due to COVID-19 increased drastically on a regular basis all around the globe, governments started to take the pandemic seriously. Governments responded by taking a range of preventive measures like the closure of national and international borders, closure of educational institutions, movie theatres, museums, parks, beaches, gyms, cancellation of cultural, religious and sporting events, bans on public transport, suspension of tourism and national lockdowns. All these measures were aimed at preventing the transmission of COVID-19 but inevitably it also led to an unpredictable and uncertain present and future. The public had many questions: When will the pandemic end? Can any of the available drugs cure COVID-19? When will a successful vaccine be developed? How soon the developed vaccine will become accessible to everyone especially to the people in the undeveloped and developing countries? Is Chloroquine effective? How important are face masks and hand sanitizers? Does COVID-19 also affect the brain and the heart? Currently, there are no certain answers and no one can predict the answers either. This current unpredictable and uncertain state due to the COVID-19 pandemic has led to fear, stress, anxiety and an increase in the rate of suicides. This paper reviews how the developments since December 2019 has led to an unpredictable and uncertain present and future and how this affects the mental wellbeing of people.

## Temporal unpredictability and Probabilistic uncertainty

Humans experience heightened stress and anxiety to unpredictable and uncertain events than predictable and certain events in life. In general, humans prefer predictable aversive events over unpredictable aversive events.<sup>4,12</sup> This fact is supported by the safety signal hypothesis which states that “when an organism can predict threat because it is signaled by a cue, the absence of the threat signal comes to predict the absence of danger, that is, safety. However, when aversive events are not signaled (unpredictable), the periods of safety are also not signaled. In the absence of periods of safety, the organism remains in a state of chronic anxiety and sustained anxious anticipation”.<sup>13</sup> The NPU threat test is widely used to assess the effect of unpredictable and uncertain threats on emotions in humans and animals. There are three different conditions in the NPU threat test: no aversive event, predictable aversive events (the oncoming aversive event is signaled by a cue) and unpredictable aversive events (the oncoming aversive event is not signaled).<sup>14</sup> Electric shocks, screams, disturbing pictures, a blast of air to the neck are some of the commonly employed aversive events in the NPU threat test. The response, the subjects’ fear and anxiety in response to predictable and unpredictable threats, is assessed most commonly by startle reflex.<sup>14</sup>

A study by Grillon *et al.* investigated the emotional responses in 72 healthy volunteers to predictable and unpredictable shocks. The results of this study revealed that unpredictable shocks produced a higher level of sustained anxiety than predictable shocks.<sup>13</sup> Shankman *et al.* examined the timing and intensity of predictable and unpredictable shocks in 115 student volunteers. Results revealed that anxiety was elevated for unpredictable timing and intensity suggesting that unpredictability plays a role in anxiety in human beings.<sup>15</sup> It has also been reported that panic disorder patients are extremely sensitive to unpredictable aversive stimuli. In this study, 18 panic disorder patients and 24 volunteers were subjected to predictable and unpredictable aversive stimuli. A heightened level of anxiety was observed in panic disorder patients in unpredictable conditions.<sup>10</sup> Anja Schmitz and colleagues examined the anxious responses to predictable and unpredictable threats in a group of 48 children and adolescents (27 boys and 21 girls; age range, 7-17). An intense blast of air was used as an aversive stimulus in this study and anxious responses were measured with the startle reflex. An increase in startle response was observed in unpredictable condition and an elevation in startle responses was also observed between cues in

unpredictable conditions compared with neutral condition indicating a sustained level of anxiety during unpredictable conditions.<sup>16</sup>

The coronavirus pandemic has affected people around the globe in multiple ways. The fear of him/her or their family getting infected and stress and anxiety about an uncertain and unpredictable present and future have affected the mental health of the population.<sup>17</sup> Social isolation and economic burden caused by lockdowns have further heightened the anxiety and stress among people. This fear and anxiety are further exacerbated by false information about the transmission of the virus, the number of infected cases, mortality rate and lack of preventive or therapeutic measures against coronavirus.<sup>18,19</sup> Past epidemics have always been associated with fear and anxiety. For instance, there was an increase in suicide rates in the US during the Spanish flu between 1918 and 1920. The suicide rate first peaked between October 1918 and April 1919, and then again in the winter of 1919-1920. These periods coincide with the first and second major wave of the Spanish flu epidemic.<sup>20</sup> Similarly, during the Ebola epidemic, an increase in psychological stress was observed among the survivors due to social isolation, daily exposure to deaths of family and friends, exposure to dead bodies, unfair treatment by the medical staff, social stigma and confusing messages regarding the transmission of Ebola from government and organizations.<sup>21</sup> An increase in suicide rate was observed among the people aged over 65 in Hong Kong during the 2003 outbreak of severe acute respiratory syndrome (SARS).<sup>22</sup> A similar trend of increase in anxiety and suicides has been reported in the current pandemic of COVID-19.<sup>23</sup> A similar trend of an increase in suicides is observed even among practicing physicians. Cuiyan wang *et al.* surveyed the general public in China through an online survey from 31 January to 2 February 2020 to assess the level of psychological impact, stress, anxiety and depression during the initial stages of the COVID-19 pandemic. Among the participants, 53.8% reported moderate to severe psychological impact; 28.8% reported moderate to severe anxiety symptoms; 16.5% reported moderate to severe depression symptoms and 8.1% reported moderate to severe stress levels.<sup>24</sup> A similar nationwide study carried out by Jianyin Qiu and colleagues received 52730 responses from China, Hong Kong, Macau and Taiwan by 10 February 2020. About 35% of the participants revealed that they experienced distress due to the current pandemic. Women and participants between 18 and 30 years of age and people over 60 reported a higher level of stress in this study.<sup>25</sup> Psychological stress in the times of epidemics can be

attributed to intense fear of contracting the disease, social stigma associated with communicable diseases, anxious uncertainty due to the invisible nature of microorganisms, social isolation and lack of preventive and therapeutic measures.<sup>23,26</sup> Sinta Gamonal-Limcaoco *et al.* carried out a survey to analyze the level of stress in people during the pandemic from 48 countries. A web based survey was sent to the study participants ( $n=1523$ ) between 17<sup>th</sup> March 2020 and 1<sup>st</sup> May 2020. The results of this study show an increased level of stress among the study participants especially among students, women and young adults.<sup>27</sup> Samantha K Brooks *et al.* have reported that quarantine during the pandemic increases the negative psychological effects like post-traumatic stress, anxiety and confusion. It has been reported in this work that the level of stress is increased when adequate information and a clear rationale is not given to the patients. The authors of this work suggest that when quarantine is deemed necessary a clear rationale for quarantine and a detailed information should be given to the patients as this could decrease the level of stress by neutralizing unpredictability and uncertainty around them.<sup>28</sup> A high percentage of distress (71.5%), depression (50%), anxiety(44.6%) and insomnia (34%) was found even among health care workers in a survey that involved 1257 healthcare workers.<sup>29</sup>

### The unexpected institution of lockdown

No one predicted the imposition of lockdowns and no one was certain about when the lockdowns will come to an end. A cross-country panel analysis reveals that lockdown has effectively reduced the number of new cases in the countries that implemented lockdown compared to those countries that did not institute lockdowns. A significant change was observed around 10 days after lockdowns and the efficacy continued to grow up to 20 days after lockdowns.<sup>30</sup> A similar study in Spain between 14 March 2020 and 25 April 2020 demonstrated a positive impact of lockdown in controlling the pandemic. The study reports that lockdown in Spain resulted in a decrease in incidence, hospital admissions, ICU admissions and mortality rates.<sup>31</sup> Although lockdowns helped in reducing the rate of transmission, lockdowns were announced unexpectedly. For instance, the lockdown was announced by the prime minister with little notice. The prime minister addressed the nation of 1.3 billion population on 24 March 2020 at 8 PM and the lockdown came into force at midnight with just four hours of notice.<sup>32</sup> This unexpected and unpredictable implementation of lockdown forced millions of poor migrant workers to walk thousands of kilometers to

reach home. Krishan Kumar *et al.* carried out a cross-sectional study to evaluate the psychological impact of COVID-19 pandemic and lockdown on migrant workers in India. About 73.5% of the participants screened positive for depression and 50% for anxiety. Among the participants 58.1% complained frustration, 55.1% complained low mood, 51 % complained irritation and 51% also complained about fear of death.<sup>33</sup> Indian psychiatry association conducted an online survey to evaluate the psychological impact of lockdown on general public. A total of 1871 replies were obtained during the survey, with 1685 (90.05%) of them being evaluated. About a quarter of the participants (38.2%) experienced anxiety, and 10.5 percent had depression. Anxiety or depression was present in 40.5 percent of the subjects. Around three-quarters of the individuals (74.1%) experienced moderate stress, and 71.7 percent indicated low well-being.<sup>34</sup> Lockdowns also cause a decrease in social integration and loneliness due to reduced access to friends and relatives and this results in anxiety and depression. The Durkheim perspective on suicide proposes that there is an increase in suicide rates with a decrease in social integration. Lockdowns inevitably result in social isolation due to closure of national and international borders, closure of educational institutions, movie theatres, museums, parks, beaches, gyms, cancellation of cultural, religious and sporting events, bans on public transport and suspension of tourism. But there was a lack of consensus and uncertainty among different countries regarding the effectiveness of lockdowns in containing the spread of coronavirus. For instance, China agrees that lockdowns helped to control the spread but Taiwan managed to control the spread without imposing a lockdown. Sweden considers lockdown an unnecessary measure and the US believes that lockdown has to be lifted very soon.<sup>30</sup> Social isolation coupled with confusions around sudden imposition and unlocking of lockdowns have further exacerbated the stress and anxiety among the public.

### **An uncertain wait for a vaccine**

In the height of COVID-19 crisis, the most important question people all around the globe had was - When will a vaccine become available for COVID-19? Most governments tried to develop a vaccine within a few months but scientists believed that it will take at least a few years to develop an effective and safe vaccine. Developing an effective and safe vaccine is a tedious process that takes an average of 10-15 years and costs between 600 million and 1 billion USD.<sup>35,36</sup> But this long and costly development process does not guarantee a

successful vaccine. For instance, no vaccine has still been developed for HIV, herpes simplex and hepatitis C even after several years of experimentation. In some cases, it took a longer than average period to develop a vaccine. For example, it took 26 years to successfully develop a vaccine for human papillomavirus and 25 years for rotavirus. To overcome this time limitation, governments and pharmaceutical companies have expedited the developmental process.<sup>37</sup> But this, in turn, has created anxiety among the public about the safety and efficacy of vaccines developed in a short period. A recent study conducted in May 2020 in the US reports that 31% of the participants revealed that they were uncertain about whether they would receive the COVID-19 vaccine when it becomes available and 20% expressed that they would choose not to get vaccinated because of the fear of safety and adverse effects.

But fortunately the vaccine discovery process against COVID-19 was very fruitful and multiple vaccines are currently approved by world health organization. The vaccine approved by world health organization are Covaxin, Covishield, Sinopharm, Sinovac, Moderna, janssen and Pfizer's RNA vaccine.<sup>38</sup> A cross-sectional study involving 1342 participants was conducted to analyze the attitude towards COVID-19 vaccination in India. This study revealed that 79 percent of those polled would take the COVID-19 vaccine while only 2% were unwilling to take the vaccine.<sup>39</sup> A similar study involving 467 participants revealed that 70.44 % were willing to take COVID-19 Vaccination.<sup>40</sup> The development of mild or major side effects following immunisation is the most important reason in vaccine hesitancy. Vaccine acceptability improves whenever more information about vaccine safety and efficacy becomes available in the public domain, preferably from a centralised, and trustworthy source. Reliable information from a centralized source decreases the uncertainty around the safety and efficacy of vaccines.

### **The chloroquine saga**

In the initial weeks of the coronavirus pandemic, chloroquine and hydroxychloroquine were touted as “wonder drugs” for COVID-19. This was based on several *in-vitro* reports that chloroquine and hydroxychloroquine inhibit the growth of novel coronavirus.<sup>41,42</sup> Chloroquine has also been reported to inhibit many viruses like Borna disease virus, the minute virus of mice, the avian leucosis virus, Mayaro virus and members of the Flaviviridae family.<sup>43</sup> The possibility that chloroquine and hydroxychloroquine could turn out to be an effective therapeutic agent against novel



coronavirus led to a sudden increase in the demand for chloroquine and hydroxychloroquine at a global level. India, the world's largest producer of generic drugs, banned the export of hydroxychloroquine and other formulations made from hydroxychloroquine but later reversed the decision.<sup>44</sup> On March 28, 2020, Food and Drug Administration (FDA) authorized the emergency use of chloroquine and hydroxychloroquine to treat adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19<sup>45</sup> and on June 15, 2020, FDA revoked the use of chloroquine and hydroxychloroquine for coronavirus infection<sup>46</sup> following reports of serious adverse effects and lack of conclusive evidence of efficacy. Preliminary results from RECOVERY trial indicate that chloroquine does not have any significant effect on mortality and also no beneficial effects on hospital stay duration or other outcomes were observed.<sup>47</sup> Another study found that hydroxychloroquine is not an effective post-exposure prophylactic against coronavirus. The incidence of a new illness compatible with Covid-19 did not differ significantly between those receiving hydroxychloroquine (11.8%) and those receiving placebo (14%).<sup>48</sup> Currently, as many as 15 drugs (Lopinavir, ritonavir, nafamostat, camostat, Famotidine umifenovir nitazoxanide ivermectin corticosteroids, tocilizumab, sarilumab, bevacizumab, fluvoxamine) are being tested for their possible therapeutic effect against novel coronavirus and all these studies are being carried out with caution so as not to repeat the mistakes made with chloroquine and hydroxychloroquine.<sup>49</sup> The projection of chloroquine and hydroxychloroquine as promising therapeutic agents in the initial days of the pandemic and the eventual failure of these two drugs as therapeutic agents has led to extreme confusion, frustration and anxiety among the public. The unpredictable wait for a therapeutic agent against coronavirus and the uncertainty of when a therapeutic agent might become available can cause stress and anxiety among the public.

### Not just a respiratory virus

Coronavirus was initially expected to affect only the respiratory tract and so it was a severe respiratory illness. But as the number of coronavirus cases increased, it came to light that coronavirus also affects other organs like blood vessels, kidneys, liver, heart and brain.<sup>50,51</sup> Patients with coronavirus also experience renal, cardiovascular, neurological, gastrointestinal and other symptoms apart from respiratory symptoms. This unpredictable outcome of coronavirus disease has caused extreme chaos and confusion among medical professionals and the public.

### COVID-19 and Variants

One of the major and worrisome features of COVID-19 pandemic is emergence of variants of SARS-Cov-2 virus. WHO has been tracking and assessing the evolution of SARS-CoV-2 in partnership with national authorities and researchers from all over the world since January 2020. The emergence of COVID-19 variants in the late 2020 posed an increased risk to public health.<sup>52-55</sup> This prompted WHO to characterize the COVID-19 variants into specific Variants of Interest (VOIs) and Variants of Concern (VOCs), in order to prioritise global monitoring and research, and ultimately to inform the ongoing response to the COVID-19 pandemic. WHO has declared alpha, beta, gamma, delta and omicron as variants of concern.<sup>56</sup> All microorganisms undergo mutations and change over time. Most often these mutations do not affect the fundamental feature of the organism. However, some mutations increase the rate of transmission, virulence, severity of disease and susceptibility to vaccines. It is important to identify the COVID-19 variants as and when they originate and communicate the information to the public to create awareness and decrease anxiety and stress among the public.

### The confusions around immunity

In general, the presence of antibodies in an individual against a specific pathogen protects them from a second infection. But in the case of coronavirus, there is no substantial evidence to prove that the presence of antibodies in an individual protects them from a second coronavirus infection.<sup>57-59</sup> WHO has informed that "at this point in the pandemic, there is not enough evidence about the effectiveness of antibody-mediated immunity to guarantee the accuracy of an "immunity passport" or "risk-free certificate" People who assume that they are immune to a second infection because they have received a positive test result may ignore public health advice. The use of such certificates may therefore increase the risks of continued transmission".<sup>60</sup>

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

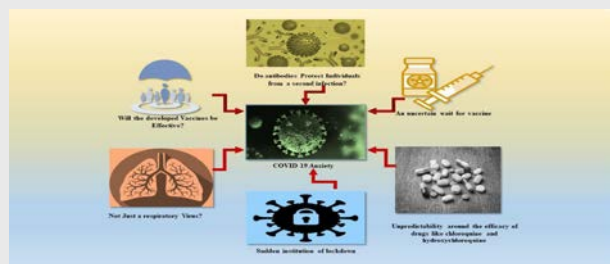
**COVID-19:** Coronavirus disease 2019; **FDA:** Food and Drug Administration; **HIV:** Human immunodeficiency virus; **ICU:** Intensive care unit; **NPU:** No shock, Predictable shock, Unpredictable shock; **RECOVERY:** Randomised Evaluation of COVID-19 therapy; **SARS:** Severe acute respiratory syndrome; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **US:** United States; **USD:** United States Dollar; **WHO:** World Health Organization.

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## PICTORIAL ABSTRACT



## SUMMARY

A predictable and certain environment is quintessential for human beings to lead a normal and stress free life. An increase in the level of anxiety and suicide rates have been observed during previous pandemics mostly due to the unpredictability and uncertainty of the social, medical and economic events during the times of pandemics. The current pandemic has also resulted in an increased level of anxiety among the public due to many unpredictable and uncertain events like sudden institution of lockdowns, uncertainty around the efficacy of therapeutic agents like chloroquine and hydroxychloroquine, an uncertain wait for vaccine, and the efficacy, availability and cost of developed vaccines.

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