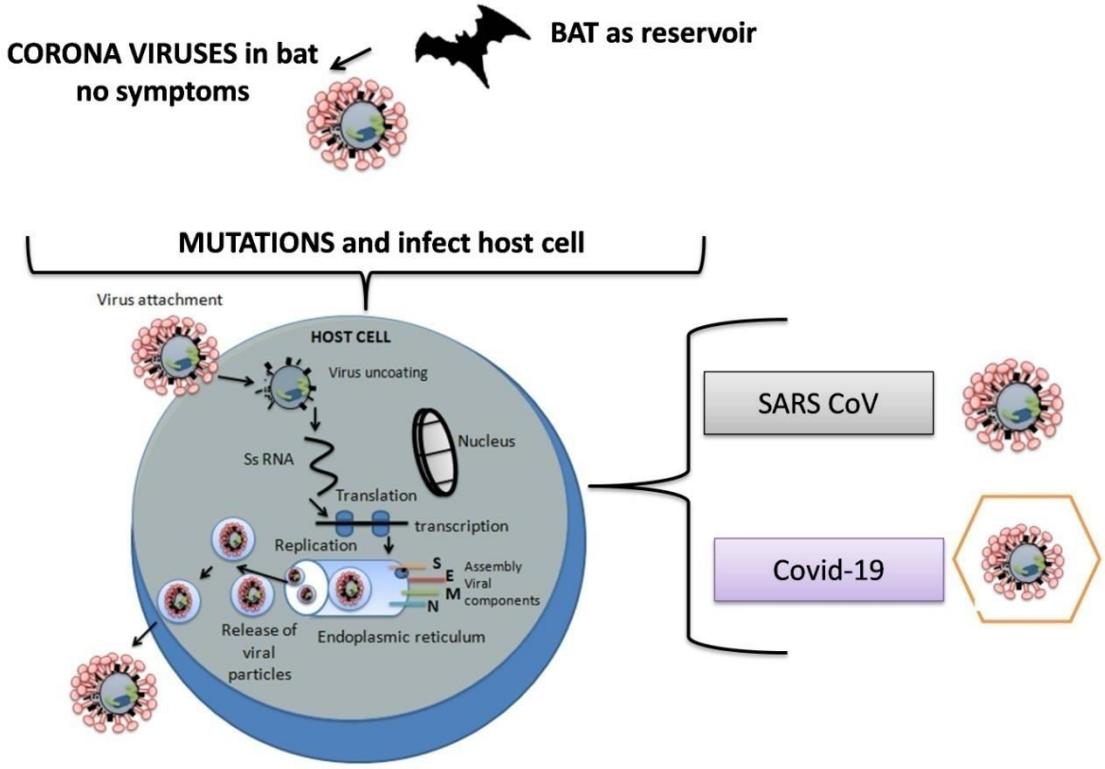
CHAPTER 1

GRAPHICAL ABSTRACT



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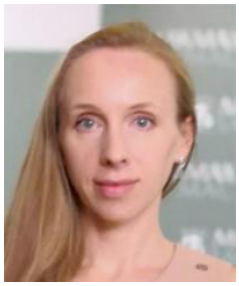

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CHAPTER-1

COVID-19: THE SIEGE OF HUMANS WITH THE INVISIBLE MICROBIAL WORLD

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ABSTRACT

The outbreak of novel coronavirus has paralyzed global activities. The zoonotic virus COVID-19 has transmitted to humans from wild species causing severe rampant on global health and economy. Currently, it has been one of the top priority research among the scientific fraternity with different scientific platforms working to develop strategies on combating COVID-19. The infection is spreading at an alarming rate and WHO has announced a global emergency and declared as pandemic situation. Undoubtedly, the emergence of the novel coronavirus is a wake-up call to control the conflict between humans and wildlife species which has led to the spillover of microbiomes causing serious implications. Surprisingly the magnitude of the infection blow was way beyond boundaries

claiming the lives of thousands across the globe. The present review emphasis the scientific literature on coronavirus and the emergence of COVID-19 with facts and influence of virus spread and transmission. The review highlights the factors promoting viral infections and preventive measures. Hence the present scenario can be easily correlated with manifestation of antimicrobial resistance which has siege emergency across the globe.

Keywords

COVID-19
PANDEMIC
MICROBIAL WORLD

1. Introduction

Viral infections of zoonotic origin are often recognized as an acute and fatal illness with high morbidity and mortality rates during its outbreaks [1,2]. These illnesses have posed a potential risk to all sectors of the world with its severe impact on global health and the economy [3]. Although the scientific fraternity is working hard to develop novel strategies to control the major impacts still the repeated occurrence of these pandemic outbreaks are clear warnings to the globe [4]. Presently, the world has witnessed yet another outbreak of the zoonotic virus which has created a pandemic situation in the form of COVID-19 [5]. The end of 2019 gave rise to a global crisis in the health care sector with the spread of the corona virus-19 which was first witnessed in Wuhan city of China [6]. Surprisingly the magnitude of the infection blow was way beyond boundaries claiming the lives of thousands across the globe [7]. There is no surprise to see such life-threatening viral infections spreading from animal to human beings as the world has witnessed in the past, for instance, SARS-Cov, MERS Cov, HIV to name a few [8]. Intuitively the emergence of novel viral infection has created pathetic conditions with no or limited choice of drugs [9]. Though these infections are causing serious health implications, the scientific community is struggling to combat such a situation [10]. There have been various factors influencing the outbreaks due to the conflicts of humans with wildlife species which are being traded and marketed as commercial commodities [11]. Apart from these, there has been a cultural shift of modern lifestyle with extensive human traveling and trekking into the wild niches which was once considered to be the zone of wild species [12]. According to the WHO database, the recent outbreaks of novel

coronaviruses are termed as life-threatening viruses for mankind [13]. Hence to overcome these situations in the near future, one must not only rely on developing novel drugs and vaccines but also concentrate on the prevention of spillover of the microbiome from animals to humans. Further, the serving of wild scrummy food can often end up in an intensive care unit owing to the consumption of undercooked food leading to such an alarming situation. There have been ignorance of early warnings from WHO which has stated that by the year 2050, antimicrobial resistance would claim the highest mortality rates compared to other diseases [14]. The present situation can be easily correlated with the manifestation of antimicrobial resistance which has siege emergency across the globe. Based on these scientific facts, the present review is drafted to highlight the importance of life-threatening microbial outbreaks as a warning for the devastation of nature eventually. The review envisages on different aspects of the coronavirus with historical importance and its brief classification coupled with preventive modes to combat such outbreaks in the near future.

2. The historical rampant spread of Coronavirus across the globe

The term corona is derived from Latin meaning crown which was designated to a group of viruses whose morphological characteristics resembled that of crown owing to their protein spikes [15]. The first coronavirus infection was witnessed in 1931 affecting avian chicken [16]. The first human infecting coronavirus (HCoV-229E) was isolated in 1965 from the nasal cavity [17]. Later, in 2003, coronaviruses gained importance due to their frequent outbreaks causing infections in the lower respiratory tract [18]. It was then the coronavirus was recognized as an etiological agent causing infections in humans in the form of a severe acute respiratory syndrome (SARS) [19]. These coronaviruses are reported to infect unciliated bronchial cells and pneumocytes [20]. Insights revealed that myriad novel coronaviruses inhabiting bats which are a potential reservoir of this virus [21]. This led to the identification of SARS coronavirus (SARS-CoV), during this outbreak, nearly 8096 SARS infection cases were reported with a staggering mortality rate of 9.6% with 774 deaths [22]. Subsequently, WHO recognized it as an epidemic that originated from China's Guangdong province and started to disseminate to other countries like Vietnam, Hong Kong, etc [23]. This outbreak indicated the evolution of the coronavirus

saga in human beings. The evolution process was also confirmed with the detection of SARS related coronaviruses from bats and other animals from the samples isolated from wild commercial markets [24].

Studies have also suggested that, in their natural reservoir, they are asymptomatic and have become virulent only when they enter different host systems [25]. The investigation highlighted that other animal-like pangolins, wild dogs, civets acts as carrier host from bats to human beings [26]. These facts commemorate the interspecies transmission and circulation of coronaviruses among various animal species has led to genetic modification causing more virulent viruses which becomes life-threatening ailment once it reaches the human beings [19,24]. As it reaches the human body, it replicates and causes infection in the super host further disseminate the disease to other individuals in numerous ways. In 2012, the emergence of the coronavirus was reported from the Middle East region which expressed the similar respiratory syndrome of previously reported SARS-CoV, the host being identified as camel [27]. The middle east respiratory syndrome coronavirus (MERS-CoV) reported to cause infection with 145 deaths and the majority of cases were reported from Saudi Arabia [28]. In the current scenario, the world has witnessed yet another infectious agent of coronavirus which is said to be novel and was identified in the city of Wuhan in late 2019. The symptoms are almost similar to the siblings of the previous coronavirus but the infection rate is rapid and elevating [29]. By the start of 2020, there was a severe outbreak of this novel coronavirus (COVID-19) which was spread to almost every country [30]. The world is reported to have been engulfed with the sign of this deadly outbreak COVID-19. However, the mortality rates of COVID-19 are reported to be lesser than the previous outbreaks but the infected numbers are on the much higher side.

3. Different strains of coronavirus reported

Coronaviruses are single-stranded RNA, enveloped, positive sense viruses that reside inside different animal cells and cause infections and they are reported to become an infectious agent as they encounter human beings [31]. These viruses belong to order Nidovirales with the family of Coronaviridae. There are nearly 26 different species that have been reported to date [32]. Broadly, the coronaviruses can be grouped into four

genera based on their host specificity and genetic composition. The alphacoronavirus: CoVs 229E and NL63. Betacorona virus includes CoVs-MERS, SARS, HKU1, OC43. Gamma coronaviruses include whale CoV and Dolphin CoV and delta coronaviruses induces white eye CoV, porcine CoV, etc [20]. The conflict between coronaviruses and human beings can be traced to 500 years as per the reports [33]. Ever since then these zoonotic pathogens are capable of causing enteric diseases. The vast genetic diversity coupled with interspecies transmission from avians to animals and to humans causing genetic recombination making them one of the world life-threatening zoonotic agents [20].

4. Structure elucidation of Coronavirus

Coronaviruses have the largest genome among the RNA viruses with size ranging from 26 to 32 kilobase pairs in length [34]. The genome codes for five important proteins such as nucleocapsid (N), envelope (E), spike (S), membrane (M) and Hemagglutinin Esterase (HE) [35]. The HE proteins are only found in beta coronaviruses (Figure.1). All these proteins encapsid and play an important role and participate to form a viral particle. These proteins huddled with each other to form interaction which forms an important virulent factor. The S-protein is found outside which gives the morphology of crown-like structure [36]. The S proteins interact with M proteins via the C-terminal membrane and the N-terminus part of the protein involves binding to the host cell [34]. The membrane protein plays an important role in the diffusion of viral particle into the host cell and also participate in generating antigenic proteins [37]. The E proteins participate in the assembly of the virus within the host cell and attachment of the viruses [38]. The N proteins aids in replication and transcription of the viruses. The N protein also helps in binding to the helix in the viral genome to form nucleocapsid [39]. Recent studies have also highlighted that the coronaviruses encode for additional proteins depending upon their host of transmission [31]. The results of early sequencing displayed the about 89% similarity of COVID-19 to its previously reported member SARS-CoVZXC21 inhabiting bat and also showed 82% similarity to human SARS coronavirus [40]. The mode of entry of the novel coronavirus is reported to have a similar route to enter the host cell as shown in figure 2. Whenever a virus enters into host its mainly by recognizing and attaching to the

receptors. COVID 19 is no exception, as per some of the recent studies ACE2 is considered as a potential portal for entry of this deadly pathogen [41]. The C terminal domain of COVID spike protein in complex binding with human ACE2 protein. This spike protein is responsible for the displayed cell tropism and hence plays a pivotal role in interspecies transmission [42]. As stated before in the paper the virus is documented to be originated from the meat market of Wuhan city of China and is now spreading across more than 200 countries as a wildfire through the human transmission.

The spike proteins C terminal domain is responsible for binding to that of the ACE2 host receptor. Further COVID -19 has shown in various structural analyses that, they are capable of using diverse receptors, thereby chaining their binding specificity multiple times making them very potent novel viruses. Once the viral spike through S protein bind to the targeted receptor, it also assists the fusion of viral and cell membrane so that the nucleic acids are routed to the cytosol of the host. Before this process priming of S protein takes place encashing a plethora of host proteases like trypsin and furin. The important components of viruses are assembled with the host cell endoplasmic reticulum coupled with Golgi complex compartments (Figure 2).

5. COVID-19 as infectious diseases and its complication

As mentioned earlier the conflict of coronaviruses with human beings are often led to an outbreak. The practices of trading wild animals and marketing for the flesh have posed risk which costs the pandemic outbreak of the novel coronavirus in November 2019 [20, 12]. The first case of COVID-19 was reported from Wuhan city of China which was stemmed from the animal and seafood market [20]. The early symptoms of this infection were similar to the previous outbreaks of zoonotic diseases like SARS coronavirus [5]. This infection gained momentum and spreading like a wildfire across different parts of China and extending to disseminate to the entire world. The impact is at an alarming rate and WHO has listed COVID-19 as one of the life-threatening diseases of recent times [12,13]. Further, the Center for Disease Control has reported that people with immune-compromised, elder population are at higher risk to acquire severe pneumonia from this virus [5,25]. Concomitantly, the infections in China also broke out targeting the younger population in the closed environment of schools and other institutions making the

situation much worse than expected [20, 12, 13]. The infection became contagious as the infection rates started to mount rapidly which has resulted to have a negative impact on the global economy and has caused huge dent economy and health care facilities across the globe.

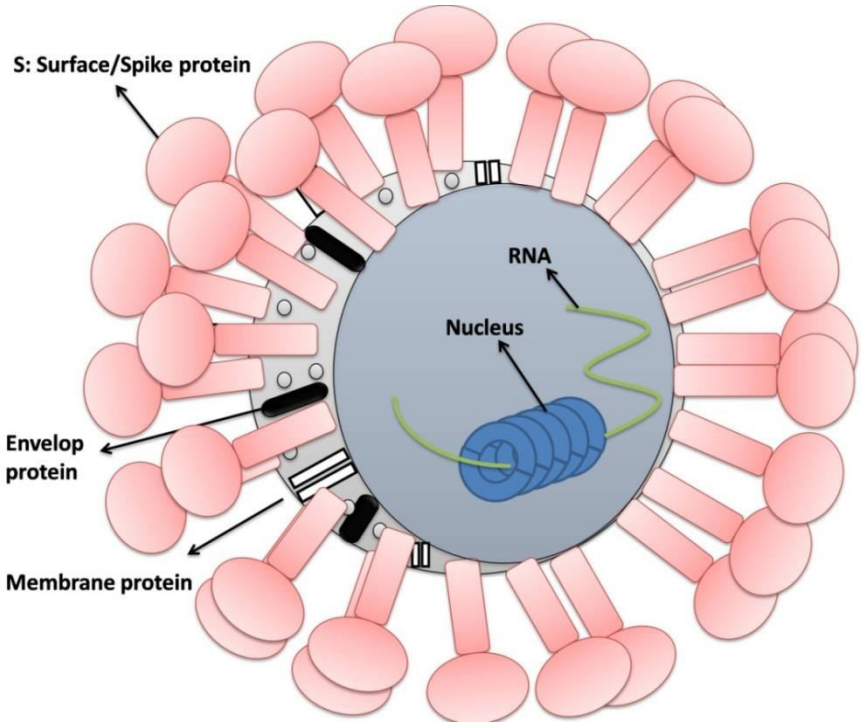

Figure.1. Structure elucidation of corona virus with respect to COVID-19

6. The symptoms and diagnosis of Coronaviruses with available tools for detection

The clinical manifestation and symptoms of coronaviruses are reported to target the respiratory system of the host by damaging the alveolar and macrophages. But studies have also confirmed that the infection is not localized to the pulmonary system [20, 40, 43]. Once the infection is initiated, the initial condition is similar to flu-like symptoms with high fever, chills, cold, body pain, etc. Further, with the increase in the infection rates, the patient may experience shortness of breath and the viral components are reported to have sufficiently replicated inside the host body to affect other parts of the body [44, 45]. This indicates the risk posed during the infection and the condition becomes severe with the individuals already suffering from health-related ailments. The infection can easily be transmitted via coughing, sneezing, and stools [5,45]. The droplets released from the

infected person forms aerosol and can reach healthy individual when comes in contact [12,13,45]. The early diagnosis of coronaviruses is problematic since the virus reaches the pulmonary system and starts replicating in host with an incubation time of 5-10 days depending upon various factors [46]. The radiographic techniques display abnormalities in the lungs only after 10 days of infections the duration varies on the severity and degree of infection [20]. The detection of infection can be done with molecular PCR assays which also depends on the titer value of viral genetic material [20]. In the majority of cases, the highest titer value of viral RNA is found during the second week of infection. Whereas, early detection during the first week is possible with sensitive PCR and sensitive enzyme immunoassay for targeted Nucleocapsid protein [47]. Further increase in the level of enzymes such as lactate dehydrogenase and creatine kinase acts as an indicator of infections which aids in detection [5,45].

7. The biotic and abiotic factors influencing the spread of COVID-19

Any disease or infections are often associated with myriad factors that influence the degree of virulence and transmission. In the case of recent outbreaks of the coronavirus from Wuhan city China, which has spread across nearly 77 countries is reported to have greatly influenced to increase the virus titer values [20]. The initial reports indicate the biotic factors like other living organisms such as reservoir host which is predicted as a bat and the carrier host claimed to be pangolins have played important roles [26, 29]. Any individuals coming in close contact with these animals have witnessed high-risk factors to acquire the infections [26]. Besides the use of wild animal flesh for consumption and the modern lifestyle of traveling has resulted in the spread of COVID-19. Early studies from scientific fraternity have reported the weakened immune response increases the viral particles in the infected hosts [20,26]. The individuals who are immuno-compromised, ailing with other medical implications such as diabetics, cardiovascular dysfunctions, renal failure, and acute respiratory diseases have posed a greater threat from COVID-19 infections [48].

This indicates the role of the immune system to act as a first-line defense towards invading the COVID-19 virus. Future impending investigations on this can lead to concrete evidence of the exact biotic factors promoting the spread of infection. Similarly, initial

claims are being made related to the temperature, humidity, and lifestyle of the populations to spread the infections [49]. As of now, early studies claim that higher the temperature coupled with increased humidity slower the transmission rate compared to the temperature below 20 degrees [49,50]. Adding to this, countries like Scandinavian nations and close to the northern hemisphere have shown the low impact of viral transmission below zero degrees [50]. The healthy lifestyles and use of garlic, ginger, green herb tea can aid in cleaning the body to a greater extent which can help in boosting the immune system to combat any viral disease [51]. The age has also played an important role in the mortality and morbidity rates with higher the age above 40 are at danger zone if encountered with the infection [6,7,51]. To claim these suggestions, further research is highly recommended to study the growth pattern of this disease concerning environmental factors.

8. The current possible drugs and vaccine to combat COVID-19

The search for best-suited drugs to combat any situation is often time-consuming and problematic since initial trails from laboratory scale to surpass the clinical trials and get approval consist of hardship. The advance scientific tools coupled with integrated medical knowledge results in the time gap of nearly 30 years for commercially available drugs. In the case of COVID-19, there have been non-stop searching at different laboratories across the globe [7,52]. There is no evidence of official use of the drug in the treatment of COVID-19 and most of the drugs are under clinical trials. Based on the clinical evidence of antiviral activity, some of the drugs are initially investigated to combat COVID-19 for instance use of Chloroquine has reported expressing in vitro activity against previously reported SARS coronavirus [53]. The use of chloroquine is based on immunomodulating properties [54]. Scientific literature suggests the inhibition of viral enzymes required for replication coupled with acidification of cell membrane and inhibits ACE2 cellular receptor which plays an important role in fusion or attachment of virus [53]. The use of hydroxychloroquine also involve similar mechanisms along with the immunomodulation of cytokine [55]. The use of ritonavir and lopinavir has displayed a vitro anti-viral properties for previously reported coronaviruses like SARS and MERS [56].

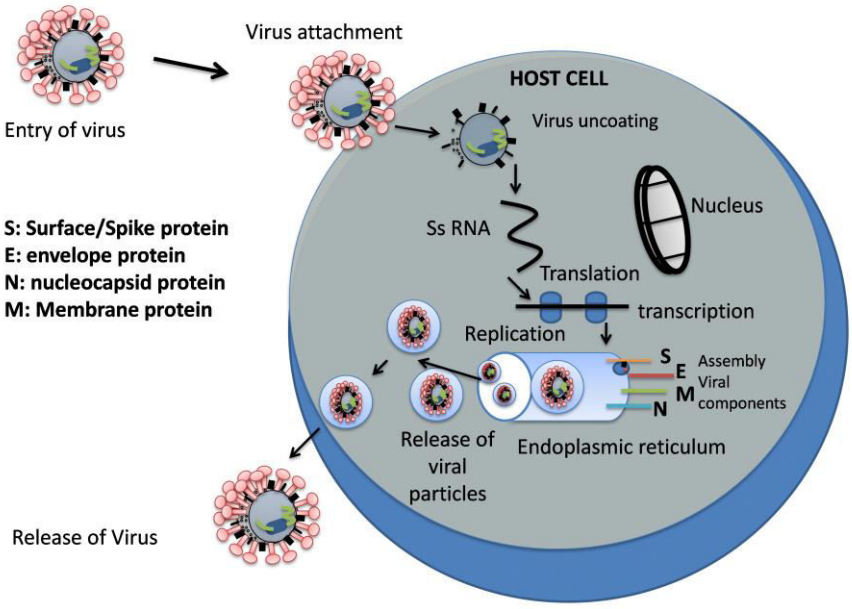

Figure.2. The possible mode of transmission of virus into the host cell

The mode of action is based on the inactivation of vital enzymes required for replication. As a counterpart, azithromycin is also tested owing to their immunomodulatory properties which can down regulate inflammatory responses and prevent the production cytokine [57, 58]. Also, to control the temperature in COVID-19 patients, acetaminophen is administered as per the initial information of the FDA. As of now, exclusive anti-viral therapy to combat COVID-19 is under investigation and further research is essential to elucidate the drug and its mode of action. To develop vaccination to the current novel coronavirus COVID-19, comprehensive knowledge of their molecular and genetic makeup must be available [59]. The complete structure elucidation of the virus and its components can be promising enough to target the virulent factors [60]. As per the initial investigations, types of proteins associated with coronaviruses whose understanding is very important [59]. The knowledge of immunology upon the exposure of the viruses can be handy to understand the first line of defense mechanisms from the host body and the recruitment of myriad cells to combat the infection can reveal the possible targets to develop the vaccine against the novel coronavirus [61]. At the same

time developing novel technologies will be handy to track the infected patients spreading the disease [62].

9. The preventive measures to combat COVID-19

In the current scenario, COVID-19 is recognized as a contagious virus that has created a global international emergency with its magnitude spreading to nearly more than 77 countries across the globe. It is for the 6th time, the global emergency declared by WHO and has designated the current situation as pandemic on January 30th, 2020 (WHO 2020). The CDC and NCIRD released a set of guidelines and measures to prevent the spread of COVID-19 (CDC 2020 and NCIRD 2020). Maintaining the social distance has resulted in controlling the pandemic situation and self-quarantine has shown a significant impact to prevent the transmission. The use of masks might be helpful to prevent the entry of airborne droplets containing viral particles. Most of the countries have sealed their entry and exit border which has prevented the further influx of foreign nationalities which might pose risk to spread the contamination. In this current situation, rapid detection kits are highly recommended to screen as much as the population to extract the number the infected individual. Further, maintaining hygienic conditions like washing hands regularly with soap/ hand wash and usage of hand sanitizer is recommended to prevent the entry of pathogens. Also, washing face and bathing twice flushes the foreign bodies and prevent the entry of invading entities. (CDC 2020, Ashour 2020). The scientific community is working on different strategies to prevent the current outbreak and hoping to combat the situation.

10. The future perspective to control viral outbreaks with COVID-19 as example

The world has to learn the lesson for their ignorance despite the previous outbreaks which created a pathetic situation in most countries especially underdeveloped countries. But this time the world's global leading countries have succumbed to the contagious novel coronavirus. The migration of the coronavirus from the wild animal as their primary host which upon encountering the secondary host becoming virulent and spreading the zoonotic infections to the human being. The rate of mortality and morbidity is without any boundaries causing the spillover of microbiomes from wild to urban niches.

In the near future, to prevent such outbreaks, there should be stringency to control the improper usage of wildlife trading and declaring the species as super host for inhabiting the etiologic agents which can cause severe outbreaks. The WHO should consider antimicrobial resistance as a global emergency and instruct the countries to develop strategies to break down such epidemic and pandemic situations. It should be of national interest to develop high equipped laboratory to diagnose the outbreak within shorter time intervals and develop rapid kits that can reach the masses and remote areas. The utilization of the skilled human resource of life science graduates who are well qualified to tackle the situation in scientific manners. Implementation of integrated scientific knowledge into the medical sector to come up with preventive guidelines will be highly essential in emergencies. No matter how much the technological advances exist, the human should not forget the existence of microbial species which are reported to the early forms of life which have made the world habitable planet and have potential to make reverse the situation upon mishandling its resource. The knowledge of Ayurveda and traditional medicines should be brought down for the commercial development of drugs to make it safer for consumption. The recent advances of nanotechnology can unfold the rapid detection tool and can be employed to develop vaccines coupled with targeted drug delivery systems. Implementing a ban on poaching wild lives for flesh and their niches for human use should be immediately brought under the scanner and should be handled to punish the culprits under international law. Finally, providing funding to the budding researcher to take up challenging tasks will guard the nations against the sudden outbreaks. Exclusive research laboratories should be set up under one roof with expertise from different scientific backgrounds.

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