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What can we learn from previous pandemics to reduce the frequency of emerging infectious diseases like COVID-19?

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ABSTRACT

The global risks report of 2020 stated, climate-related issues dominate all of the top-five long-term critical global risks burning the planet and according to the report, “as existing health risks resurge and new ones emerge, humanity’s past successes in overcoming health challenges are no guarantee of future results.” Over the last few decades, the world has experienced several pandemic outbreaks of various pathogens and the frequency of the emergence of novel strains of infectious organisms has increased in recent decades. As per expert opinion, rapidly mutating viruses, emergence and re-emergence of epidemics with increasing frequencies, climate-sensitive vector-borne diseases are likely to be increasing over the years and the trends will continue and intensify. Susceptible disease hosts, anthropogenic activities and environmental changes contribute and trigger the ‘adaptive evolution’ of infectious agents to thrive and spread into different ecological niches and to adapt to new hosts. The overarching objective of this paper is to provide insight into the human actions which should be strictly regulated to help to sustain life on earth. To identify and categorize the triggering factors that contribute to disease ecology, especially repeated emergence of disease pandemics, a theory building approach, ‘Total Interpretive Structural Modeling’ (TISM) was used; also the tool, ‘Impact Matrix Cross-Reference Multiplication Applied to a Classification’ analysis (MICMAC) was applied to rank the risk factors based on their impacts on other factors and on the interdependence among them. This mathematical modeling tool clearly explains the strength, position and interconnectedness of each anthropogenic factor that contributes to the evolution of pathogens and to the frequent emergence of pandemics which needs to be addressed with immediate priority. As we are least prepared for another pandemic outbreak, significant policy attention must be focused on the causative factors to limit emerging outbreaks like COVID 19 in the future.

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1. Introduction

Emerging Infectious Diseases (EID) and spreading of diseases, and vulnerability to pandemics and disease outbreaks have been

increasing locally and globally during the last few decades (Lindahl et al., 2015). An EID, by definition is “a disease which has a tendency to spread geographically; cause an increased incidence of disease, or infect a new species or new populations; or is a disease spreading within any host population” [1–4]. The increasing risks of exposure, increases in the number of susceptible individuals, and the infectiousness of the infected individual are the parameters that must be considered in assessing the risks of an EID.

Researchers have documented that, approximately one new human infectious disease has emerged per eight months on average. Since 1980, more than 35 EIDs infecting humans emerged [5]. As we are exposed to large-scale outbreaks and global pandemics, like Ebola, Sika, Swine flu, SARS, MERS and currently COVID

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19, we are at greater risk in having deaths of thousands or millions of humans and of having huge socio-economic losses [6,7].

During the 2014–16, Ebola epidemic, over 11,000 deaths with approximately 28,000 infected people, and the Severe Acute Respiratory Syndrome (SARS-CoV) of 2002–2003 with infected people in more than thirty countries on five continents infected 8000 people and caused 774 deaths. The Middle East Respiratory Syndrome Corona Viruses (MERS-CoV) caused 866 humans deaths. All three of these EIDs were 'zoonotic'.

The novel Corona Virus Disease, 2019, COVID-19 was officially designated as a pandemic by the World Health Organization (WHO), 2020; [8], has spread to 190 countries and territories, infected, 31,869,225 people and caused more than 977,057 deaths, globally as of 23rd September 2020 [9].

Even though the Corona Virus-2 (SARS-CoV-2) belongs to the family 'Coronaviridae', as SARS and MERS, shares more than 79% homology with SARS-CoV [10], the word 'novel' has been used as it is totally new in humans. It is very important to note that, many of the viruses causing EIDs were not known before, and although the diagnostic capabilities and health care have improved tremendously, an outbreak of a pandemic will cost thousands to millions of human, lives, billions of dollars and months to years to develop a safe, effective vaccine against it [11].

Currently, the entire human population is facing a global shutdown due to COVID-19. It is important to understand the key risk factors or triggers of human disease pandemics. By analyzing the major causative factors of repeated pandemic outbreaks using Total Interpretive Structural Modeling (TISM), the authors of this paper investigated the key risk factors that trigger changes leading to the emergence of virulent, pathogenic strains of emerging infectious diseases, their evolution and human susceptibility.

The author's objectives are included in the Research Questions (RQ):

RQ1: What are the major risk factors which contribute to the disease ecology of emerging infectious diseases?

RQ2: What are the relationships among these factors?

RQ3: Can these factors be ranked according to priority?

The authors of this paper evaluated the major causative factors which were found to be influential in the repeated emergence of pandemics in the context of COVID 19. Although, there are several studies suggesting the pandemic emergence and anthropogenic causes; there is an urgent need to use an integrative analytical approach to mathematically model the inter-relationships and dependency of factors to be able to prioritize them more effectively in order to take necessary actions to prevent future emergence of infectious diseases (EIDs).

2. Literature review

Although, the triggering factors for the rapid emergence of mutated, novel strains of infectious pathogens that have caused serious disease outbreaks in the last two decades were documented [12], a comprehensive analysis to characterize the inter-relationships among them is urgently needed. Fourteen of the most likely factors that influence disease ecology of emerging infectious diseases and repeated pandemics were selected for this research as highlighted in the following sections.

2.1. Emergence of zoonotic diseases

A zoonosis is any disease or infection, microbial or viral, that is naturally transmissible from vertebrate animals to humans; thus, in nature, animals maintain zoonotic infections. Looking at the

pandemic outbreaks of the last few decades, it is evident that approximately 75% of emerging diseases including the major pandemics like, HIV, Ebola virus, Zika, avian & swine influenza, SARS-CoV, MERS and the COVID-19 were all zoonotic in origin [13–17]. Zoonotic pathogens in comparison with non-zoonotic, were found to be twice as likely to emerge, especially viruses and protozoa [18–20]. Of the reported zoonotic diseases in humans, 44% were caused by viruses [21].

The pathways of zoonoses have not yet been analyzed comprehensively and quantitatively. The increasing imbalance created in the human-animal-ecosystem interface, increases the potential risks of zoonoses. Wild-life hunting & trading, interactions between wild and domestic animals and wildlife species adapted to human-modified environments [22,23], migration of infected wild birds, transportation of infected domestic or farmed animals, and loss of biodiversity, have contributed to the 'spill over' and spread of zoonotic diseases and persistence of respective pathogens. Pathogens have evolved from closely related species, for example, in the case of HIV (Chimpanzees to Humans) or by species which are distant from humans in genetic homology, but having close contact as part of animal farming or exposure in the wild, have resulted in transmission of disease causing pathogens from wild animals to humans.

Bats were the vectors of the Nipah virus to human and, SARS was transmitted to humans from bats and civet cats [24,25]. Humans were infected by Swine flu- H1N1 from pigs and birds [26]. The current pandemic COVID-19 is supposed to have been transmitted to humans from animals of Wuhan fish market [27]. The genome analysis shows that SARS-CoV-2 is 96% identical to a bat corona virus [28], but the exact source has not been confirmed yet. When viruses spread via multiple hosts, the chances of viral mutations are high and the resulting evolution of novel strains of pathogens with pandemic potential are higher.

2.2. Pathogen evolution and pandemic potential

Diverse factors are responsible for the evolution of a pathogen into an infectious agent which can adapt in multiple hosts and ecological niches, thereby, making it more virulent to humans (Fig. 1). The 'evolvability' of a virus, is contributed by the mutation rates of its genome which help the virus to create anti-immunity in the host. It helps the virus to jump from one host to another and also supports or increases its replication rate inside the host and virulence [29–31].

Rapid mutations are an important adaptation for pathogens as it results in their evolution and spreading among the same types of hosts and jumping to other host species. The absence of proof reading capacity of viral RNA replicases can generate swarms of genetic variants of progeny viruses which undergo selection pressures for fitness to bypass the host's immune system [32]. These mutations include mutations in the viral genome which helps it to overcome the host's immune surveillance and other host resistant factors which interfere with their replication inside the host cell. The adaptive mutations also strengthen host-specific receptor structure modifications to ease cellular entry to new host species. Viral genetic recombination or re-assortment is another factor contributing to virulence. The co-infection of closely related viral species in the same host cell can also have a role in the emergence of new viruses by re-assortment [33,34].

Environmental factors like changes in climate and habitat can trigger changes in reservoir host populations or intermediate insect vectors, which can contribute to evolution of the pathogen and result in disease emergence, such as in the case of Lyme borreliosis (LB) which, spread as a consequence of reforestation, habitat loss and climate change. The Lyme disease is caused by a spirochete in

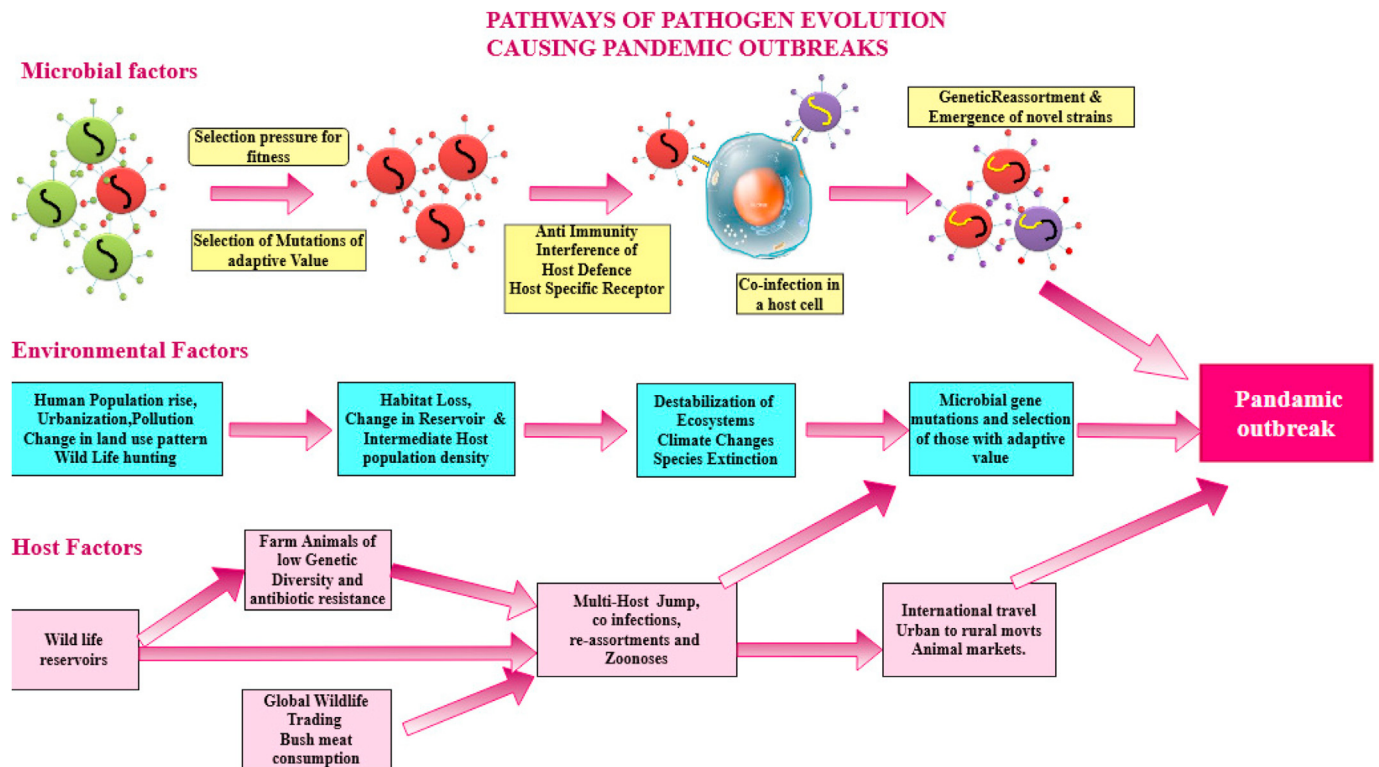


Fig. 1. Graphical abstract showing the common pathways of pathogen evolution in pandemic outbreaks.

Several factors contribute to the adaptive evolution of infectious agents to spread into different ecological niches, adapt to new hosts, escape from host defense mechanisms and spread globally. They are broadly categorized in three major factors; host factors, microbial factors and environmental factors (Fig. 1). Rapid genetic mutation is an adaptation for pathogen evolution and emergence. Viral genetic recombination or re-assortment is another factor contributing their degree of virulence. The co-infection by closely related viral species in the same host cell can have a role in the emergence of new virus strains by re-assortment. Environmental factors like changes in climate, habitat etc along with host factors can also trigger changes in reservoir host populations or intermediate vectors which can contribute to pathogen evolution and emergence of epidemics or pandemics.

the genus 'Borrelia' which, shuttles between an arthropod vector, usually a tick, and a mammalian, usually deer or avian populations. In the last century, deforestation as part of industrialization followed by reforestation resulted in fluctuations in deer populations due to reduction in predator species and hunting. This changes in the 'pathogen's host populations' triggered the emergence and re-emergence of Lyme disease [35]; tick-borne encephalitis (TBE) and malaria [36,37] in USA and Europe.

The risk factors associated with new viral pathogens in humans are related with its epidemic potential and the severity of physical symptoms it causes. Transmissibility of a virus or 'the average number of new infections generated by an infected person in a totally naïve population' is expressed as 'the basic reproduction number' (R_0). To establish in a new host species the virus must have an $R_0 > 1$. If it is below 1, the virus cannot be sustained in the host species for long and it gradually disappears. The mean R_0 of the current viral outbreak COVID-19 was found to be 3.28, which means that it is very infectious [38].

2.3. Host susceptibility to pandemics

Host defence patterns are as important as the mutation and evolution of the pathogen in emergence of virulent strains. The immune-competency of the host is an important factor of infections [39]. More research should be done to understand the species barrier, such that, pathogens are harmless to their natural hosts, while they can cause serious damage to other species [40]. Several factors influence the host's susceptibility to an epidemic. For example, chemotherapy for cancer, age, underlying diseases,

obesity related diseases, malnutrition and chronic infections are important factors that influence viral impacts. Host's defences may be reduced by immune-suppression due to diseases like HIV/AIDS or 'iatrogenic' or medicine induced immune-mediated diseases and transplantation and is well documented with COVID 19 [41]. Lack of proper vaccinations and cross-immune protection (For example, yellow fever and dengue fever; smallpox and monkeypox etc exhibits cross protection) can also contribute to increased susceptibility of a host to a newly emerging pathogen [19,42]. The cross-immunity among the different strains of an infectious agent or among different pathogens can reduce the replication of a pathogen inside a host, emergence and spread of novel viruses.

Changes in global travel patterns and migration can accelerate the spread of diseases [27]. Changes in the host's sexual behavioral patterns (HIV/AIDS) and the host's genetics, i.e. loss of genetic diversity in massively inbred monocultures of livestock can increase the host susceptibility or the potential for invasions by new pathogens [43].

2.4. Human food consumption habits

Wild-life hunting and trading of animals of many species are consumed by humans. The wild life meat or 'bush meat' is a primary food source, in places like Congo basin. Several species such as chiropteran flying foxes, carnivores, artiodactyls or ungulates, primates, pangolins, rodents, aves and reptiles are hunted for human consumption, in southeast Asia, especially in the Indo-Chinese peninsula (Tordoff et al., 2005; WCS, 2013; [44]. Bush meat hunting increases the interactions among humans and wildlife, which

creates a key path for transmission of diseases like SARS, Ebola, SARS-CoV-2 etc [45]. Ebola outbreak in the Congo Basin and Gabon in 1990s was linked to humans being exposed to and eating wild primates like chimpanzees and baboons. Some research documented that human acquisition of SARS was from civets in 2002 [46,47], Nipah from flying foxes [48] and MERS-CoV from bats [49].

Urban wildlife markets are increasingly popular in many parts of the world and the animals and their products traded globally can increase the chances of disease transmission [50]. Bat consumption is a major threat as they are natural reservoirs of several viruses, like corona viruses [51], which are transmitted to humans directly from bats or through intermediate hosts [52]. Approximately, 5700 viruses associated with bats had been identified from 207 bat species identified from 77 countries [53]. Bat meat is considered to be delicious cuisine in many cultures who consume 56 species of bats [52,54]. In the case of COVID-19, bats are the primary suspects from which the pathogen might have transferred to humans as the genome analysis showing 96% similarity between bat corona viruses and human corona virus-2 [28].

2.5. Industrial farming of livestock and monoculture effects

Escalating global demands on the production of high-protein/high-energy animal feed resulted in intensified animal production. Commercial large-scale, industrial farming operations for production of dairy products, meat and other animal products are increasing risks of zoonotic disease transmission. Such monocultures often have negative impacts on animals that are grown or raised in suboptimal conditions without properly addressing the inherent issues of waste management and animal welfare [55]. High-density monocultures enhance the growth of zoonotic pathogens due to reduced host resistance. Whereas in the wild, due to broader genetic diversity, this infectious agent is less likely to spread as rapidly, often ends in limited number of hosts; this leads to lower potential for it to cause a pandemic [56,57].

Reduction of genetic diversity among livestock, mixed species cultures (like pig farm, cattle farm and poultry together), loss of traditional breeds, and antibiotic resistance, influence the genetic evolution and cause the emergence of zoonotic pathogens easier. When livestock are exposed to wild species which are natural reservoirs of several pathogens, if 'spill over' happens from a wild species to a suitable host with high densities and very little genetic variability, the pathogen may flourish in the new host [58–60]. For example, the 1998–1999 Nipah virus outbreaks in Malaysia, once the virus crossed from wild fruit bats to high-density domestic swine farms with very small genetic diversity, an explosive outbreak of the Nipah virus resulted in widespread exposure of humans [61]; [62]. Similarly, it has been documented that the avian influenza virus was happened to be transferred to huge monocultures of poultry by contact from wild bird populations carrying the virus.

Unsustainable use of resources, water and air pollution caused by the waste products and methane gas production, biocide and fertilizer manufacture and use for feed production, etc, make industrial farming a potential triggering factor to global environmental degradation. Deforestation for planting monocultures for feeding livestock results in habitat losses and reduced species diversity and greater susceptibility to plant and/or animal disease epidemics or pandemics [63,64]. Transforming a species diverse tropical rain forest into a monoculture of coconut palms or soybeans or sugarcane, makes the monoculture vulnerable to new strains or types of pathogens, reduce species diversity and gradually ecological instability may happen.

2.6. Emergence of antibiotic resistance in livestock

The use of antibiotics is a significant concern in contemporary livestock production. Antibiotic usage in livestock is very common because they protect the animals from diseases and death due to infections. Repeated use of antibiotics causes elimination of a number of resident strains from the host's gut, leading to the gradual emergence of antibiotic resistant pathogen strains. Natural host microbial communities and their diversities are important as they have a protective effect, as it suppresses the growth of resistant pathogenic microbial strains.

Since 1940, 40% of emerging infectious diseases identified in Asia documented the emergence of a new pattern of antimicrobial resistance [6]. According to the WHO, excessive use of antibiotic drugs in human and animals result in a post-antibiotic era where pathogens of treatable diseases come back as more virulent. In addition to the overuse of antibiotic drugs, growing human population and climate changes contribute to antibiotic resistance [65,66]. The routine prophylactic use of antibiotics in crowded, unhealthy, conditions may decrease animal infections, but at the same time the microbial diversity within the livestock may be reduced and antibiotic resistant superbugs will be selected. For example, Methicillin Resistant Staphylococcus Aureus (MRSA) transmission from pigs to humans and Swine-associated MRSA can cause an invasive disease in human patients [67,68]. So antibiotic resistance in livestock may act as catalysts for development of zoonoses, which can spread out of control.

2.7. Expanding human population

Global human population is growing about 1.1% or about 83 million net increases per year, consequently, anthropogenic environmental destruction, species diversity losses, and climate changes are all interconnected. Human population increases have impacts on globalization as the lack of resources, increases global marketing of Fast-Moving Consumer Goods (FMCG). Global labor employment, enhances human migration that accelerates spreading of infectious diseases. It can improve public health, medical, agriculture, industrial and allied technologies as international assistance to populations has been found to be helpful in meeting the demands of people and in helping to reduce the gap between rich and poor countries, but inequity among and within countries continues to increase globally [69].

Human population explosion and globalization have increased inter-connectivity and migration, opening global markets for wildlife trade, which enhances the spread of zoonotic pathogens globally. Increasing human populations are causing increased strains on the resources, increasing civil unrest, and war & famine, all of which contribute to political and ecological migration of people. These migrants, who often live-in high-density slums or inhabited forest lands increase the probability of human–animal contact and accelerate global spread of zoonotic diseases. As human population density increases, greater crowding and contact rates occur with increase in contaminated air and water that catalyzes spreading of infectious diseases [70]. These pressures also have impacts on the ecosystem services due to changes in land-use patterns, deforestation, increased fossil carbon footprints of urbanization, that result in ecosystem destabilization and to climate changes that accelerate the evolution and spreading of pathogens and their vectors [71,72].

2.8. Globalization

Better communications, knowledge transfer, cultural and scientific exchanges, increasing wireless trade and investment flows,

mass media, international living standards, improved transport, etc., have facilitated human migration [73]. Human population mobility is always linked with epidemic events as it increases the rate of transfer of pathogens and vectors into new areas (Morens et al., 2008). The dynamic interactions of the populations showing differences in genetics, environmental, socioeconomic, or behavioral patterns, between the migrant and host populations (Ampel, 1991) are often be the determinants of the general well-being of both migrants and their hosts.

The quote that: “in the case of a severe global pandemic, the world is only as prepared as its weakest country,” is true in the sense that air travel can spread a disease around the planet in a matter of hours as country's security is interdependent.

Globalization has had an impact on the worldwide trade of animals for food and products, pets, zoos, scientific education and exhibitions, and tourism. This global movement has increased the potential for the translocation of zoonotic diseases, which cause serious effects on animal and human health [74]. It is not uncommon that the animals that are imported, often pose substantial risks to human health. For example, in 2003, the monkeypox disease was introduced in to United States, when African Gambian giant rats were shipped along with prairie dogs [75]. That was similar to the cases of human tularemia and salmonellosis outbreaks that were connected with prairie dogs and hedgehogs [76,77]. Wildlife trade has flourished by the interconnected global markets which facilitate rapid worldwide dissemination of diseases that also pose threats to biodiversity by speeding up the processes of species extinction and environmental degradation.

2.9. Interconnectedness & human migration

As the concept of ‘the global village,’ has become a reality, the interconnectedness and human migrations have increased tremendously. There are different types of migration such as counter-urbanization, internal migration, rural/urban migration-emigration/immigration, and, international migration. Human migration can be triggered by many causes such as local socio-economic-political issues, sea-level rising causing disappearance of islands or low-lying continental regions, or to seek ‘better lives’. Global connectedness enables diseases to spread in humans several times within their incubation period before symptoms develop. The global spread of COVID 19 was accelerated due to international airline and ship travel [78,79].

Global interconnectedness also increases international wildlife trade and accelerates the spread of zoonotic diseases due to open global markets for wildlife trade. The most dangerous thing to happen is the rapid dissemination of a pandemic, around the world irrespective of origin, because the entire world is inter-connected by modern travel measures [27].

2.10. Human habitation of naïve environments

Human habitation of naïve, untouched, unexploited, resource-rich environments can be for many reasons. High human population density, political instability and social conflicts, disasters and successive migration, wild life trade, industrial farming, modern agriculture, etc are responsible for destruction and fragmentation of naïve ecosystems, which harm the natural naïve habitat of wild animals and plants.

Losses of islands, wet-lands, plains and natural forests due to human habitation, are having strong impacts on ecosystems. These changes displace resident species by limiting their habitats and food sources, which encourage the introduced species to out-compete native organisms and to gradually displace them. When the human populations expand into previously uninhabited naïve

terrains, they come in contact with wild animals which carry organisms naturally, and can cause diseases in man. For example, Lassa fever, an acute viral disease found endemic in West African countries of Sierra Leone, Nigeria, Liberia, and Guinea, was transmitted to humans because people destroyed the forest and converted the land to intensive agricultural production [80]. There, the humans contracted the virus from forest rodents whose habitats had been destroyed for mono-cultural agricultural purposes. The Lassa fever spread by contact with the feces of infected rodents [81].

Additionally, human habitation to naïve environments increases the frequency of wildlife consumption and trading and thereby, changing the human-animal interfaces which potentiate the emergence/reemergence of zoonotic diseases and their spread via global wildlife markets [21,82–85]. Even then, as in ebola, patterns of EIDs are highly contextual and variable regionally and locally due to divergent and dynamic economic, ecological, and sociopolitical reasons.

2.11. Civil unrest

The civil unrest in a country can weaken the strength of health care systems or the health security of a nation and can delay the early detection of a disease outbreak. There is a direct correlation between civil unrest areas and emerging infections, as was documented in SARS in Southern China and the H1N1 flu in Mexico. Other examples include the Ebola and Nipah outbreaks that illustrated how social disruption and the threat of violence can trigger people to migrate to naïve forest lands, where they rely on nontraditional foods, animals such as bats, rodents, or primates, which can greatly elevate the risk of zoonotic spillover [86].

Civil unrest can increase the chances of human to human infectious disease transmissions through poor hygiene and sanitation facilities in refugee camps, compounded with malnutrition, poor health and delay in early detection of an epidemic [87–89]. For example, the West African Ebola outbreak exposed gaps related to the timely detection of that disease. It was officially declared in 2016; three years after the first case had been reported. By then, the disease had heavily affected Guinea, Liberia and Sierra Leone. It infected more than 28,000 people and killed 11,300. The devastated political, economic and health care systems compounded with security challenges of these countries reduced their outbreak surveillance and control capacities [90].

2.12. Urbanization and carbon footprint

The loss of biodiversity due to the fragmentation of habitat or shifting landscapes may result in the rise of zoonoses as happened in the reforested north-eastern United States and in virgin forests of agro-ecosystems in the Central Valley of Costa Rica [91,92] when deforestation and hunting reduced the number of the predator populations that resulted in a rapid increase in the deer population in reforested lands that increased the arthropod population that is the vector of the Lyme disease in deer. It is important for societies to better understand consequences of such complex inter-connectedness.

A carbon footprint is defined as “the total greenhouse gas (GHG) emissions caused by an individual, event, organization, or product, expressed as carbon dioxide equivalent”; the predominant cause of global warming and climate change [93,94]. According to reports, China is the world's largest CO₂ emitter contributing about 25% (9.8 billion metric tons in 2017) followed by USA, 15% and EU-28 with 10% [95].

Urbanization followed by commercialization and industrialization increases the usage of fossil fuels. Although urban areas cover

only 0.4–0.9% of the global land surfaces, they contribute 70% of carbon emission causing increases in the earth's atmospheric temperatures, that are resulting in dramatic climate changes in increased frequencies and severities of catastrophic weather events, flooding, water shortages and disturbed ecosystems. In addition to urbanization, globalization, human habitation to naïve environments, deforestation, habitat losses, pollution and the resulting destruction of nature and consequent imbalances, all contribute to increased carbon footprint impacts that are causing climate changes and global warming.

Global warming causes changes in the epidemiology of infectious diseases by influencing three factors. Changes in behavior and susceptibility of the human host population, changes, in the abundance and distribution patterns of vector populations, and the genomic changes of causative infectious agents. Changes, in the climate may cause crop failures and famines that result in malnutrition and reduced host resistance to infections. Compounding this, higher temperatures may shorten the extrinsic incubation periods of pathogens like dengue and yellow fever viruses leading to more rapid epidemic/pandemic spread. All these contribute or trigger human migration to better places of suitable climatic conditions [96].

Researchers' report that, as the earth warms, some vector populations like mosquitoes causing Malaria, Dengue and ticks carrying viruses causing encephalitic syndrome etc may expand into new geographic areas, whereas others may disappear; which means, vector populations are likely to shift to temperate regions [97]. One of the examples for this is ZIKV, a flavivirus, which is transmitted to humans primarily through the female, *Aedes aegypti* mosquito. Similarly the change in water ecology due to global warming may also reflect on the epidemic spread of Cholera in the northern temperate countries as it emerged as pandemics for seven times in the last two centuries spreading from Asia to Europe, Africa, and North America [98].

2.13. Illegal wildlife trade

Illegal wildlife trade is unlawful harvest of and trade in live animals and plants or parts and products derived from them. It is a multibillion-dollar business [99]; the fourth most lucrative global crime after drugs, humans and arms, in which wildlife is traded as skins, leather goods, exotic pets, food, cultural or traditional medicine and in many other forms [100–103].

Wildlife trade also increases the human-wild life interface and increases human exposure to wildlife vectors, that increases the risks of EIDs as in COVID 19 [104] where bats were the reservoir of COVID-19 and to the pangolins that are suspected to have been the most probable intermediate host, in the same way that another coronavirus – the 2002 Sars outbreak – moved from horseshoe bats to cat-like civets before infecting humans [105,106]. Pangolins are reported to be the most trafficked animal in the world, especially in south-east Asia where they are an endangered species [105,107].

Over exploitation of wildlife has a negative effect on species survival and biodiversity. Wildlife trade is the second most important cause of species extinction after habitat losses. Illegal massive, wildlife trade has greatly reduced key species' numbers in many ecosystems, resulting in imbalances and reduced diversity and set the stage for disease pandemics [108].

2.14. Destabilization of the ecosystems and climate changes

The magnitudes of damages caused by human-induced climate changes are more dangerous than its quantitative effects, as it is irreversible [109]. As climate change, diversity of disease vectors is

increasing and they are spreading to new geographic zones. For example, in the USA and Europe, the changes in distribution patterns observed in vector-borne diseases, such as tick-borne encephalitis (TBE), malaria and Lyme disease or Lyme borreliosis (LB) was associated with human impacts on the landscape that triggered tick populations to multiply significantly by increasing both their habitat and wildlife hosts, which led to the emergence of LB in USA and Europe, with high transmission rates [35–37,110]. Climate changes and intensification of animal farming are important causes of imbalances to the human and animal ecosystem interfaces.

Beyond intensive agriculture, in other ecosystems, decreased biodiversity can increase the transmission of pathogens if the density of reservoir hosts increases due to reduced predation and competition [111–115]. For example, in the United States, the incidence of West Nile encephalitis was supposed to be due to low avian diversity [116]. The collective consequences of the negative human interference on the balance of nature, due to deforestation, air and water pollution, over exploitation of biotic and abiotic resources, extensive usage of fossil-carbon based energy sources that release millions of tons of greenhouse gases, that are causing climate changes, and in turn accelerating the spread of diseases into new regions of the world.

3. Research methodology

Interpretive Structural Modeling (ISM) [117] is a theory building approach used to analyze the interrelationship among the factors in complex situations. ISM is a structural model which indicates how these factors are linked in a hierarchical manner. The overall structure of the factor's relationships are captured in a graphical model. Any theory building approach should address the basic questions of what, why when and how [118]. The ISM approach answers to the what, why and when questions, but it is lacking of 'how' these relationships are happened. ISM is developed further by Sushil [119] as Total Interpretive Structural Modeling (TISM). The TISM answers the question 'how'. TISM approach articulates the interrelationship between factors and detailed interpretation among the factors are captured. The 'what' question has been answered by the identification of the causative factors that were found to be influential in the disease ecology of repeatedly emerging infectious diseases through literature sources, 'how' and 'why' question has been answered by the capturing the interrelationships among factors and hierarchal structure of factors using TISM approach.

Singh and Sushil [120] have strived to model different factors of 'Total Quality Management' that act as enablers in improving airline performance, using the TISM technique. Sagar et al. [121], have used TISM to explore the relationships between various factors that have a significant influence on the loyalty of customers in the area of cloud computing. Likewise, Shibin et al. [122], have explored the use of the TISM technique so as to study factors that both facilitate and hinder the occurrence of flexible green supply chain management. Likewise, Balaji and Arshinder [123] have attempted to understand the factors responsible for wastage of food, in the context of the Indian food chain of perishable nature. The TISM technique helps the researchers to create a network of relationships between various factors, something that subsequently allows them to understand the inherent structural nature of the model. Sehgal et al. [124], also have used TISM to model the most critical factors responsible for the success of virtual network operators in the mobile platform, in the context of the telecommunication market in India.

Sindhvani and Malhotra [125] has used the TISM technique to identify enablers of the agile manufacturing system and to study the interactions between these enablers. Manjunatheshwara and

Vinodh [143] have studied the relationships between some of the most significant factors that are responsible for the advancement of tablet devices in a sustainable manner, using the TISM technique. Yeravdekar and Behl [126] also have used the TISM technique in order to create a standard model of reference, while studying diverse factors influencing management education in India. Sandeepa and Chand [127] have used the TISM technique to understand the interactions between various factors of flexibility in a supply chain that is sustainable.

The TISM approach has been applied over the years, has found use in a diverse stream of applications for analysing interrelationships among factors [128–130], but until now it has not been used to investigate causative factors of emergence and re-emergence of epidemics and pandemics. The research tool TISM was used to obtain insights into the interrelationships among factors that trigger frequencies of emerging infectious diseases and their increased spreading from epidemics to pandemics.

To identify and categorize the triggering factors that contribute to disease ecology, especially repeated emergence of disease pandemics, a theory building approach, “Total Interpretive Structural Modeling,” (TISM) was used to obtain insights into the interrelationships among factors that trigger frequencies of emerging infectious diseases and their increased spreading from epidemics to pandemics. Many researchers have used TISM to analyze interrelationships in manufacturing and service industries [128–131], but until now it has not been used to investigate causative factors of emergence and re-emergence of epidemics and pandemics. The tool, ‘Impact Matrix Cross-Reference Multiplication Applied to a Classification’ analysis (MICMAC) was applied to rank the risk factors based on their impacts on other factors and on the interdependence among them. This mathematical modeling tool clearly explains the strength, position and interconnectedness of each anthropogenic factor that contributes to the evolution of pathogens and to the frequent emergence of pandemics which needs to be addressed with immediate priority.

The flowchart of steps involved in TISM approach for analyzing the causative factors that were found to be influential in the disease ecology of repeatedly emerging infectious diseases is shown in Fig. 2.

The following steps were used by the authors of this paper, based upon research performed using TISM by Ref. [132–135]:

- 1. Identification of the factors:** The first step was to identify the factors that cause repeated emergence of pandemics. The factors, listed in Table 1, were identified through literature review and from expert opinion.
- 2. Interpretation of relationships among factors:** In the TISM approach, this step answers the question, ‘how’, and is designed to help researchers to understand how Factor 1 influences Factor 2. The relative strength of relationships was represented on a scale between 0 and 4 in ascending order of strength. For this study, 25 responses were obtained from professors, scientists and researchers in life sciences in India. The respondents were selected on the basis of their backgrounds, especially in biomedical research or in teaching Eco-biology.
- 3. Initial Reachability Matrix (IRM) was used to establish interconnectedness among factors:** To arrive at the Initial Reachability Matrix (IRM), the contextual relationships among the factors had to be determined. The IRM represents the direct relationships among factors. For instance, it is needed to see whether a certain factor ‘A’ has an influence on the qualitative nature or the quantitative value of another factor ‘B’. If there is a strong or very strong influence, then ‘1’ is entered in the appropriate cell of the initial form of the reachability matrix. Else, ‘0’ is entered. To aggregate the responses of individual

experts, mode is used as a method of compilation. Table 2 presents the IRM that represents the direct relationships for the causative factors which were found to be influential in the disease ecology of emerging infectious diseases.

- 4. Developing the Final Reachability Matrix (FRM) after checking for transitivity:**

This process allows checking for transitivity that has been caused because of inference, between some of the pairs that are a part of the reachability matrix initially created. A transitivity check must be done before arriving at the FRM to find the significant relationships, among factors which were not directly represented in the IRM. The transitivity check was performed on all entries with ‘0’ in the IRM. 1* or 1** signifies the presence of transitivity, and the lack of it means that the original value of ‘0’ can be retained. 1* implies first level transitivity wherein if $P = Q$ and $Q = R$ then $P = R$. 1** implies second level transitivity wherein if $P = Q$, $Q = R$, and $R = S$, then $P = S$. Table 3 presents the FRM that was determined for this paper.

- 5. Partition of the factors from FRM into different levels:** In this step, the FRM was partitioned into three sets. The first set, called the reachability set, was comprised of the row elements of the final reachability matrix. The second set, called the antecedent set, was comprised of the column elements of the final reachability matrix. The third set is called the intersection set, and it was comprised of common elements of the previous two sets. In Iteration-1, the intersection elements were ‘one’ and indicate reachability set. These factors were removed from the set and designated as level-1 factors. The process was repeated until the partitioned reachability matrices were obtained at various levels.
- 6. Interaction matrix derived from direct and transitive links:** From the expert opinion, the significant transitive links were drawn, which are highly influential relationship links among the transitive links of the FRM. The interaction matrix was developed by using the direct links as well as the transitive links that were significant. Interaction matrix representing the direct and significant transitive relationships of the causative factors which were found to be influential in the disease ecology of repeatedly emerging infectious diseases as depicted in Table 4.
- 7. Creating the digraph and the TISM model:** At the final level, an entity known as the digraph, an acronym for directed graph, was created. The contents of the FRM as well as the level partitions were used for this purpose. After the digraph was developed, the direct and the significant transitive links were used to derive useful conclusions. The factors at the top of the model were called the first level factors. Subsequently, going down the digraph, the numeric value of each level increases in ascending order, one at a time. Then, using results from the interpretative matrix and the digraph, the TISM model was developed. The TISM model representing the direct and significant transitive relationships of the causative factors which were found to be influential in the disease ecology of emerging infectious diseases contains eight levels. The level eight is the base level, if any changes happened in the level-VIII factors (F4) may reflect in all other factors. The level-VII factors can influence all other factors except level-VIII factors. Likewise the factor’s impact is on upward direction; i.e., the factors in the bottom levels determines the performance of those factors in the top levels

The model prepared using the TISM approach alone, is shown in Fig. 3. The interpretative-interaction matrix, that summarizes qualitative notes about the direct as well as the significant transitive links, is shown in Table 5.

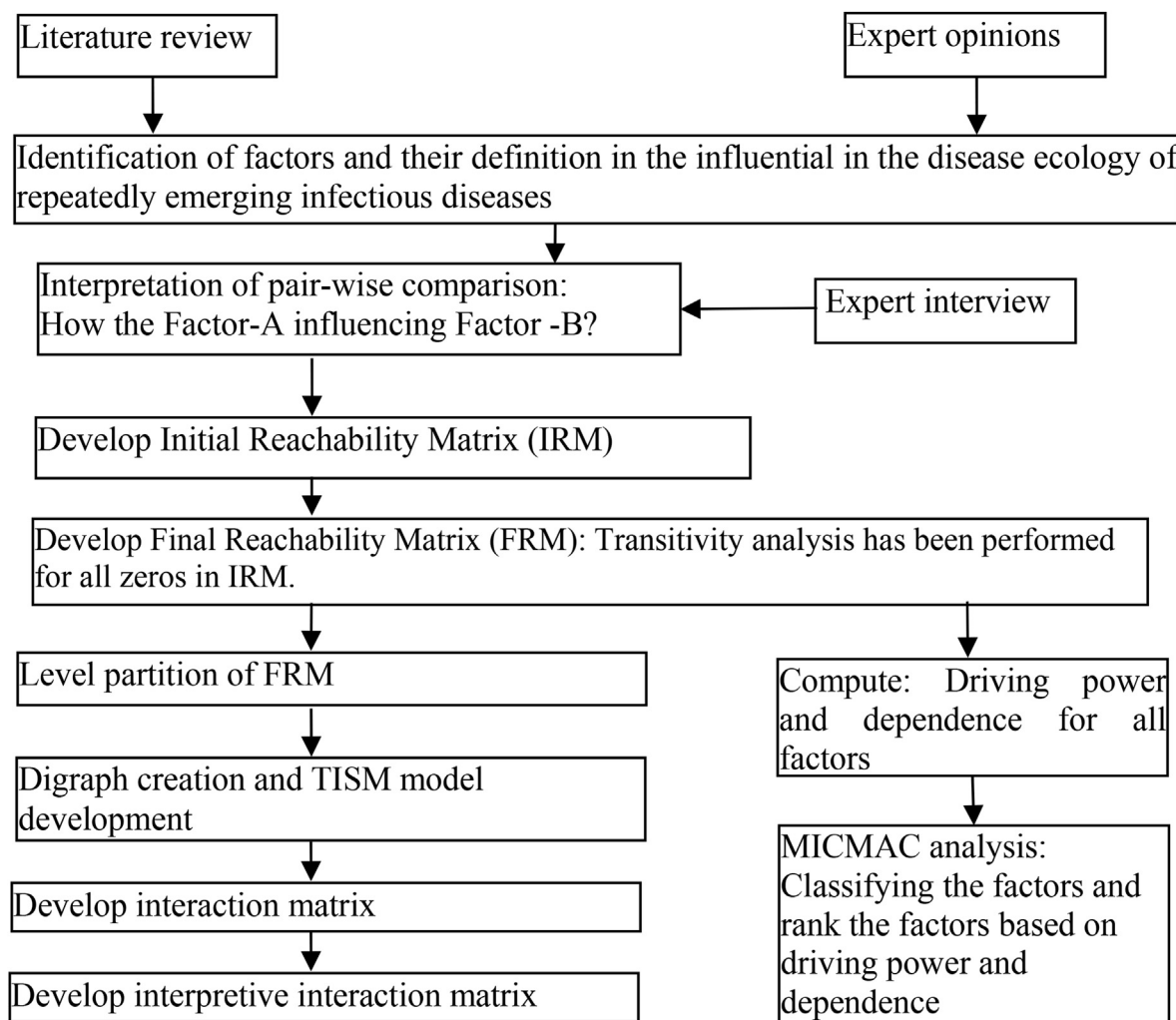


Fig. 2. Flow of TISM for causative factors that were found to be influential in the disease ecology.

Table 1

Identification of factors and literature sources of the causative factors that were found to be influential in the disease ecology of repeatedly emerging infectious diseases.

Sl. No.	Factors
1	Emergence of Zoonotic Diseases (F1)
2	Destabilization of Ecosystems & Climate change (F2)
3	Illegal wildlife trade (F3)
4	Expanding human population (F4)
5	Urbanization & Carbon footprint (F5)
6	Human habitation to naive environments (F6)
7	Industrial farming of livestock & monoculture effect (F7)
8	Emergence of Antibiotic resistance in livestock (F8)
9	Interconnectedness & Human migration (F9)
10	Globalization (F10)
11	Civil Unrests (F11)
12	Pathogen evolution and pandemic potential (F12)
13	Host susceptibility to Pandemics (F13)
14	Human food consumption habits (F14)

Table 2

Initial Reachability Matrix (IRM) prepared, represents the direct relationships for the causative factors which were found to be influential in the disease ecology of emerging infectious diseases.

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
F1	1	0	0	0	0	0	0	0	0	0	0	1	1	0
F2	1	1	0	0	0	0	1	1	0	0	0	1	0	0
F3	1	1	1	0	1	0	0	0	0	0	0	1	0	1
F4	1	1	1	1	1	1	1	1	1	1	1	0	0	1
F5	1	1	1	0	1	0	1	0	0	0	0	1	0	1
F6	1	1	1	0	1	1	1	0	1	0	0	0	1	1
F7	1	1	0	0	0	0	1	1	0	0	0	0	1	0
F8	1	0	0	0	0	0	0	1	0	0	0	1	0	0
F9	1	0	0	0	1	1	0	0	1	0	0	0	0	0
F10	1	1	1	0	1	0	1	0	1	1	0	0	0	1
F11	0	0	0	0	0	1	0	0	1	0	1	0	0	0
F12	1	0	0	0	0	0	0	0	0	0	0	1	1	0
F13	0	0	0	0	0	0	0	0	0	0	0	0	1	0
F14	1	0	1	0	1	0	1	0	0	0	0	0	1	1

4. Results and discussions

4.1. Interpretation of the TISM di-graph presented in Fig. 3

TISM Di-graph is the graphical presentation of the TISM analysis representing the direct and significant transitive relationships of

the causative factors which were found to be influential in the disease ecology of emerging infectious diseases. The Di-graph was prepared based on the interaction matrix included in Table 4.

The Di-graph represented eight levels of interdependence, starting with increasing human populations (F4) on the bottom level (level VIII) of the pyramid representing the root cause of all

Table 3

Final Reachability Matrix (FRM) prepared by including the significant transitive link factors involved in the disease ecology of emerging infectious diseases.

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
F1	1	0	0	0	0	0	0	0	0	0	0	1	1	0
F2	1	1	0	0	0	0	1	1	0	0	0	1	1*	0
F3	1	1	1	0	1	0	1*	1*	0	0	0	1	1*	1
F4	1	1	1	1	1	1	1	1	1	1	1	1*	1*	1
F5	1	1	1	0	1	0	1	1*	0	0	0	1	1*	1
F6	1	1	1	0	1	1	1	1*	1	0	0	1*	1	1
F7	1	1	0	0	0	0	1	1	0	0	0	1*	1	0
F8	1	0	0	0	0	0	0	1	0	0	0	1	1*	0
F9	1	1*	1*	0	1	1	1*	1**	1	0	0	1*	1*	1*
F10	1	1	1	0	1	1*	1	1*	1	1	0	1*	1*	1
F11	1*	1*	1*	0	1*	1	1*	1**	1	0	1	1**	1*	1*
F12	1	0	0	0	0	0	0	0	0	0	0	1	1	0
F13	0	0	0	0	0	0	0	0	0	0	0	0	1	0
F14	1	1*	1	0	1	0	1	1*	0	0	0	1*	1	1

*, ** represents transitive links.

Table 4

Interaction matrix representing the direct and significant transitive relationships of the causative factors which were found to be influential in the disease ecology of repeatedly emerging infectious diseases.

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
F1	1	0	0	0	0	0	0	0	0	0	0	1	1	0
F2	1	1	0	0	0	0	1	1	0	0	0	1	1*	0
F3	1	1	1	0	1	0	1*	0	0	0	0	1	0	1
F4	1	1	1	1	1	1	1	1	1	1	1	0	0	1
F5	1	1	1	0	1	0	1	0	0	0	0	1	0	1
F6	1	1	1	0	1	1	1	0	1	0	0	0	1	1
F7	1	1	0	0	0	0	1	1	0	0	0	0	1	0
F8	1	0	0	0	0	0	0	1	0	0	0	1	0	0
F9	1	0	1*	0	1	1	0	0	1	0	0	0	0	1*
F10	1	1	1	0	1	1*	1	0	1	1	0	0	0	1
F11	0	0	0	0	0	1	0	0	1	0	1	0	0	0
F12	1	0	0	0	0	0	0	0	0	0	1	1	1	0
F13	0	0	0	0	0	0	0	0	0	0	0	1	1	0
F14	1	1*	1	0	1	0	1	0	0	0	0	1	1	1

* represents significant transitive links.

other factors studied by the authors of this paper, that trigger changes listed in the topmost level (level 1) of the pyramid, the host susceptibility to emerging pandemics (F13).

The interpretive interaction matrix of the causative factors found to be influential in the repeated emergence of pandemics is presented in Table 5.

To summarize, exponential growth of the human population' (F4) plays key roles in the transformation of local epidemics in to pandemics, depending upon the disease-causing agent's virulence and host susceptibility. The human population increase is leading to climate changes, globalization (F10) and civil unrest (F11) as the pressures on resources limit their supply, therefore, global markets for labor and products, along with technological advancements have dramatically increased human migration, globally. The human population explosion also triggered socio-economic and political struggles and civil conflicts, due to increasing poverty caused by worsening inequities, risks to health as well as increased food and safe water insecurities in many countries.

From time immemorial, population growth has served as an impetus for exploration and colonization, exploitation of geological and ecological resources as well as human resources has that often has led to or was based upon civil unrest, war, famine, infectious disease outbreaks among the natives, that, in-part triggered, caused mass migration. Trade, foreign investment, and migration tend to rise with increased human capital. Many dimensions are interconnected with and migration (F9) and encourage wildlife trade (F3) in global markets. These dynamics help to enable a pathogen to be spread globally in a short time.

Human migration either due to civil unrest or as part of globalization, lead to human habitation in naïve environments (F6), either for habitation or for industrialization and urbanization; which gradually destroy the regional ecological balance by over-exploitation of nature through anthropogenic activities like, deforestation, intense agriculture, mining, industrialization, air, water and soil pollution, urbanization and rapidly increasing carbon foot prints (F5).

Changes in food consumption patterns (F14), 'bush meat' consumption and wildlife trade and exposure of farm animals and humans to wild animals increase human-animal interactions and increase the likelihood of pandemics (F13), and often result in the emergence or re-emergence of independently re-assorted zoonotic (F1) pathogens after repeated infections in different hosts or co-infections of similar microbial strains in the same host.

Industrial or factory farming of livestock and their monoculture effects (F7), with little genetic diversity, increase the probability that new pathogens or new strains of previously encountered pathogens may be strengthened by new capacities derived while in wild species hosts.

Loss of bio-diversity is a trigger to virulent pathogen emergence when natural reservoir hosts face threats to their existence and adaptation in multiple hosts and related mutations of significant survival value. Large scale habitat destruction and changes in land utilization patterns, pollution and poaching, result in habitat losses, decreases in species diversity and number, shifts in reservoir hosts of pathogens, species extinction, that may converge to result in severe ecological destruction, ecosystem de-stabilization and climate changes (F2). The climate changes and ecosystem imbalances combined with intensive agriculture frequently results in increases in antibiotic resistant strains in farm animals and in humans. The interspecies adaptability of infectious agents and adaptive mutations of the microbial genome to gain multi-species adaptability and immune surveillance inside the host may trigger the pathogen to achieve pandemic potential (F12).

4.2. Impact Matrix Cross-Reference Multiplication Applied to a classification (MICMAC)

4.2.1. Analysis

The MICMAC analysis involves classifying the relevant causative factors into four different zones, namely: driving factors, autonomous factors, dependent factors and linkage factors [136–141]. The factors for this article were classified as:

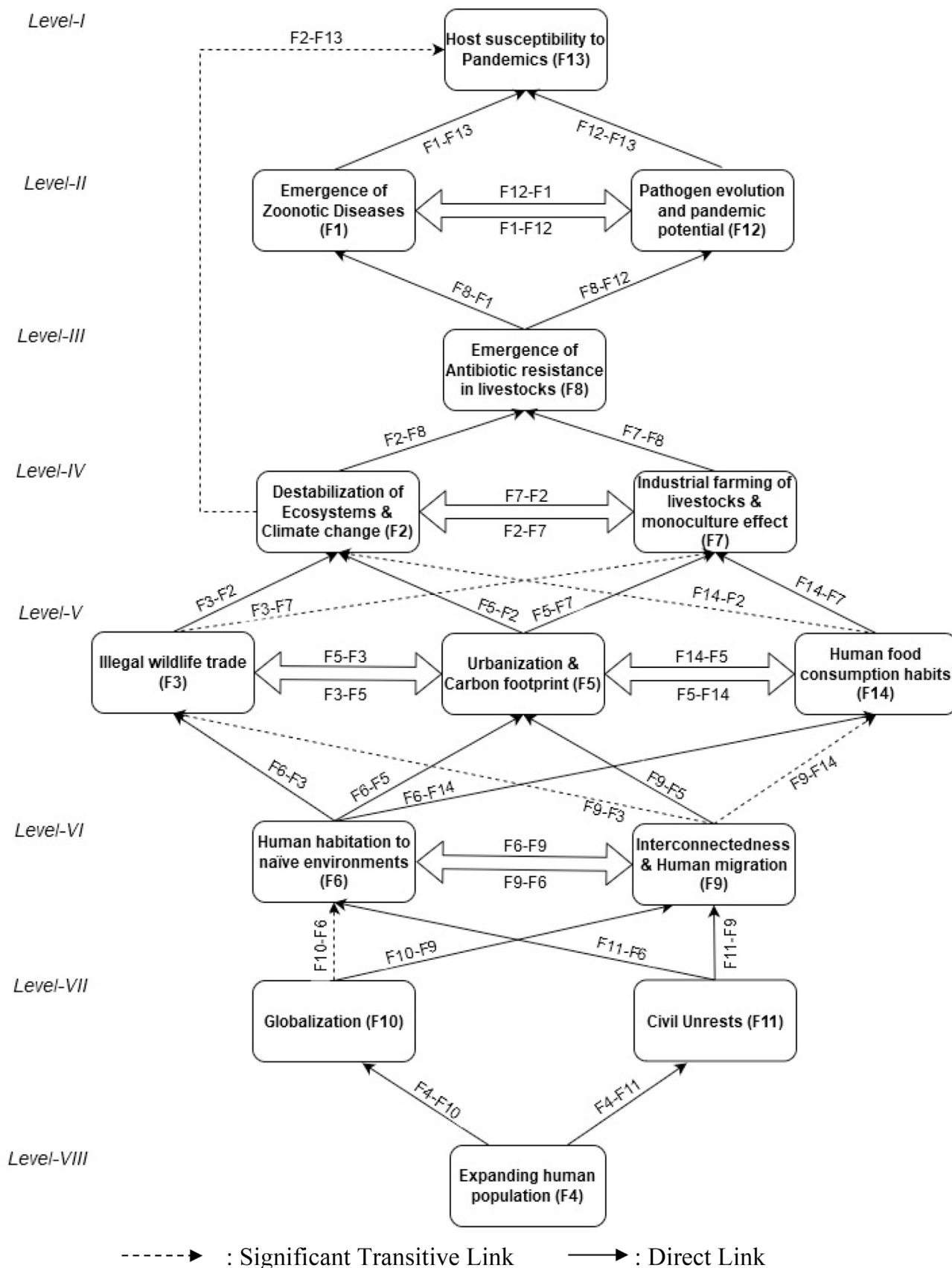


Fig. 3. TheTISM model representing the direct and significant transitive relationships of the causative factors which were found to be influential in the disease ecology of emerging infectious diseases.

Table 5

Interpretive interaction matrix representing the direct and significant transitive relationships of the causative factors which were found to be influential in the disease ecology of emerging infectious diseases.

	F1	F2	F3	F4	F5	F6	F7
F1							
F2	Climate change, especially average rising temperatures trigger emergence of zoonoses; Destabilization of ecosystems cause changes in the reservoir or vector species' diversity and the number of pathogens						Climate change can severely affect the health of factory-farmed livestock, also high temperatures speed up generation and spread of antibiotic resistance. Destabilization of ecosystems can increase human exposure to wild animals.
F3	Wildlife trade in global markets exposes multispecies to new contexts, thereby, supporting re-assortment of viruses and emergence of pandemics	Changes in reservoir species and loss of species diversity results in adaptive mutations of pathogens			Global markets and urban food habits increase wildlife trade and bush meat consumption		Industrial farming may not be sufficient to meet modern food consumption needs, so wildlife hunting and trading may increase
F4	Expanded population is the root cause of rapidly expanding human inhabitation of forests and wild land masses that results in increased human-animal interactions and emergence and spreading of zoonotic diseases	Human population explosion has a pivotal role in destabilization of the ecosystems and in triggering climate changes due to increased global anthropogenic activities	Human population explosion and lack of resources drive people to depend on wildlife hunting and trading.		As human population increases, urbanization increases to meet the needs of the masses, deforestation, species diversity losses, increased air and water pollution and increased fossil-carbon footprints, all of which result in increased carbon dioxide concentrations in the atmosphere that is leading to increased average global temperatures, increased severities of drought, flooding and increased severity of storms.	Increases in human populations drive people to wild, naïve forest areas in search of resources and areas for habitation.	Industrial farming of plants and livestock are needed to meet the increasing human population's needs and wants.
F5	Urbanization and pollution lead to the emergence of disease vectors and to epidemics becoming pandemics. High carbon footprints may upset the natural balance of the environment, and trigger emergence and spreading of new strains of disease-causing agents.	Urbanization, pollution, over-exploitation and increased carbon footprints cause ecosystem destabilization and climate changes	Modern, global food markets, demand wild life cuisines, especially in east Asian countries, which results in expansions of global wildlife trade.				To meet the urban demands, industrial farming using monocultures are necessary. Livestock farming, export and international marketing are integral parts of modern urban cultures.
F6	F1 Human inhabitation in naïve environments increases human –animal interactions resulting in the emergence of zoonotic diseases and the spreading of them via epidemics and pandemics.	F2 Habitat destruction and loss of biodiversity due to anthropogenic activities are having devastating effects upon ecosystem stability and are triggering climate changes	F3 Naïve habitation increases wildlife hunting for food and animal produce and increased international trade of them or of products derived from them.	F4	F5 Migration to naïve habitats may initiate urbanization followed by pollution and increased carbon footprints.	F6	F7 Naïve inhabitation may lead to deforestation of the forested land and utilization of the land for industrial farming and monocultures of plants and animals.
F7	Lack of genetic diversity supports the emergence, multiplication and	Industrial farming may cause deforestation, habitat losses and					

Table 5 (continued)

F8	dissemination of new pathogens or new strains of pathogens that have been previously present in that region.	destabilization of ecosystems leading to increased severities of climate changes				
	Antibiotic resistance results in enrichment and re-assortment of pathogens that may support or cause the emergence of new or recurrent zoonoses.					
F9	Interconnectedness facilitates the dissemination of a disease from being localized in a region to being spread globally and causing pandemics such as COVID 19		Interconnectedness has extensively enhanced global trade of wildlife		Migration to different habitats accelerates anthropogenic activities for urbanization and increases carbon footprints	Migration to naïve land masses is part of globalization and industrialization that is often interdependent upon tourism
F10	Globalization opens markets for wildlife trade, coupled with travel and migration that catalyze emergence and spreading of infectious diseases from animals to humans.	Globalization resulted in changes in habitats due to urbanization and industrialization that has caused destabilization of ecosystems and expanded climate changes.	Wildlife trade has increased dramatically in recent years due to global markets and international connectivity. As a result, human-animal interactions have dramatically increased.		Globalization and technical advancements heightened the growth of urbanization & industrialization resulting in increased carbon footprints, decreased species diversity and increasing climate changes.	Enhanced by globalization and increased demands for resources, people are increasingly inhabiting naïve forest lands and previously untouched land masses
						Increased human populations and resultant globalization requires more food and food products with international markets, expanded factory farming of livestock.
F11	F1	F2	F3	F4	F5	F6
		.				F7
						Civil unrest can result in socio-economic conflicts and lack of social security may drive people to inhabit wild and naïve land areas.
F12	Pathogen evolution by mutation, re-assortment, co-infection of related species, and interspecies transmission, can make a pathogen more virulent. Human or livestock exposure to wild reservoirs may result in the emergence of a new zoonotic disease					
F13						
F14	Bush meat harvesting, handling and consumption are risky the pose high risks for being infected by zoonoses.	Modern food consumption habits threaten wildlife extinction due to overexploitation leading to species extinction and to destabilization of ecosystems and climate changes.	Wildlife hunting is a primary source of food in many parts of the world and wildlife trade is the second most significant of species extinction. Global markets are available for bush meat.		Food consumption habits of modern urban societies pose risks to the environment; deforestation for farms and other anthropogenic factors that also increase carbon footprints and accelerate climate changes.	The accelerating demand for animal is resulting in factory farming of livestock in monocultures or in mixed farms.
F1	F8	F9	F10	F11	F12	F13
					Inter species jump of pathogen induces mutation and pathogen evolution	Industrial farming, bush meat consumption and travel, increases host

(continued on next page)

Table 5 (continued)

F2					Pathogens in a destabilized ecosystem undergo mutations, and if there is a change in reservoir species due to environmental destruction, the pathogen may evolve into a new strain that can inhabit a new ecological niche and can survive in new climatic conditions, thus making it a more flexible, highly adaptive and virulent disease agent.	susceptibility to Zoonosis Ecosystem damage can severely affect human existence. Climate changes can have negative impacts upon human immune response for ex. COVID-19 in temperate countries (as innate immunity in nasal mucosa or mucosa associated lymphoid tissue (MALT) is low in cold climates)	
F3					Wild life trade of multiple species together in markets results in re-assortment of viral genome when closely related pathogens co-infect in the same cell and finally emergence of pandemics like COVID 19		Wild life is hunted and traded mainly for food and animal produce. In some areas of the world, wild life consumption is a part of their culture
F4	F8 As human population and intensive farming increase, diseases also increase, and thus antibiotic usages and antibiotic resistant strains of pathogens are increasing in humans and livestock.	F9 Human population increases trigger human migration to better places due to lack of resources and high rates of unemployment.	F10 Human population increases and lack of resources may increase global labor supplies and product markets; exchange of medical, industrial, scientific technologies, migration and global travel of humans.	F11 Expanding human populations and lack of resources may lead to civil unrest. Socio-economic-political conflicts, disasters, poverty, war and famine and result in mass migration.	F12	F13	F14 Lack of food results in search to find new food sources, especially in the wild. Several outbreaks in Africa of, for example the Ebola in the Congo basin and SARS in east Asian countries weredue changes in food habits, specifically, increased consumption of 'bush meat' Urban culture has extensively changed human food consumption habits. In certain cultures, wild hunted meat and wild produce have become parts of their luxury cuisines.
F5					Urbanization, pollution, changes in vector species emergence, may result in pathogen evolution due to mutations and re-assortments thereby, enhancing their pandemic potential.		
F6		Human inhabitanace in naïve land masses may provide migrants more suitable places to live.				Human –animal interface and low health security may increase the onset of infectious diseases and weakening the host's immunity.	In naïve habits of food consumption habits may have to be adapted to the available resources like wild produce and bush meat.
F7	F8 Excess antibiotic usage in animal farms and hospitals results in the increase in antibiotic resistantpathogens in livestock and humans.	F9	F10	F11	F12	F13 Animal farms are the major sources of almost all recent pandemic outbreaks, as they acquire a pathogen from a wild reservoir and after repeated mutations may result in the emergence of new, more virulent strains that are also capable of infecting humans.	F14

Table 5 (continued)

F8					Resistant pathogens in repeated infections in multiple hosts may undergo adaptive mutations making them more virulent with high pandemic potential.	
F9						Migration may influence food consumption patterns based on the place, availability of food and food culture. Changes in food consumption habits have been documented to be part of globalization and exposure to diverse cultures
F10	Globalization enhanced interconnectivity and human migration as global labour openings and world markets has increased along with the spread of medical, agricultural, industrial and allied technologies					
F11	Civil unrest can induce or be based upon poverty, malnutrition, poor hygiene practices and poor health security which may drive people to seek better places to which they migrate.					
F8	F9	F10	F11	F12	F13	F14
F12					Adaptive mutations of pathogens, especially mutations which help them to adapt to various hosts and ecological niches, and to escape from host immune surveillance systems, can help them to out compete host defense mechanisms and cause infections, depending on the immune system's status of the hosts.	
F13						
F14					Wildlife purchasing, handling of meat and consumption, make humans highly susceptible to zoonoses. Also, food consumption behaviors can contribute the basic health and immunity of the hosts.	

1. *Autonomous factors (Zone-I)*: Factors that have weak dependence power and weak driving power are known as autonomous factors. In this study, there was no autonomous factor.
2. *Dependent factors (Zone-II)*: Factors that have higher dependence on other factors but lesser driving power are known as dependent factors. In this study factor 2 (destabilization of ecosystems & climate change), factor 7 (industrial farming of livestock & monoculture effect), factor 8 (Emergence of Antibiotic

- resistance in livestock), factor 1 (emergence of zoonotic diseases), factor 12 (pathogen evolution and pandemic potential) and factor 13 (host susceptibility to pandemics) were found to be dependent factors. These factors are influenced when there are changes in other factors.
3. *Linkage factors (Zone-III)*: Factors that have a strong dependence power and strong driving power are known as linkage factors. They establish the connections between the dependent and the

driving factors. In this study factor 3 (illegal wildlife trade), factor 5 (urbanization & carbon footprint) and factor 14 (human food consumption habits) were found to be the linkage factors.

4. *Driving or Independent factors (Zone-IV)*: Factors that have a strong driving power, but weak dependence power are driving factors or independent factors. In this study factor 4 (expanding human population), factor 10 (globalization), factor 11 (civil unrests), factor 6 (human habitation to naive environments) and factor 9 (interconnectedness & human migration) were found to be the driving or key factors.

As per the MICMAC analysis, causative factors found to be influential in the repeated emergence of pandemics are ranked in Table 6.

Fig. 4 represents the MICMAC graph of the causative factors found to be influential in the disease ecology of emerging infectious diseases. It depicts the driving power-dependence diagram based on the MICMAC analysis shown in Table 5.

Table 6 shows the ranking of the causative factors which were found to be influential in the repeated emergence of pandemics based on the MICMAC analyses. According to the ranking, factor 4 (expanding human population), factor 10 (globalization) and factor 11 (civil unrests), are the top key factors. Additionally, factor 6 (human habitation to naive environments) and factor 9 (interconnectedness & human migration) are highly significant, key factors.

Host susceptibility to pandemics F13 is the factor that is ranked eighth in the MICMAC analysis which means that, it has higher dependence on other factors. This is due to the fact that the changes in other factors can bring about changes in the host susceptibility to pandemics.

5. Conclusions

The authors identified fourteen risk factors that influence pandemic re-emergence through literature review and based upon data from expert's opinions. The TISM approach was used to list the factors influencing the emergence of infectious diseases and to identify the links among them. Factors were ranked according to their order of importance and a hierarchy was established using the MICMAC analysis. The results revealed that changes in any individual factor in the study could directly or indirectly help to cause repeated epidemics. Expanding human populations, globalization, and civil unrest were the top factors. Also, human habitation of naive environments and interconnectedness and human migration were found to be driving or key factors according to this model. These factors were independently and interdependently found to impose a strong impact on the increased frequency of emergence of epidemics.

Anthropogenic factors leading to ecosystem destabilization and climate changes were found to be the primary driving causes that lead to the emergence of infectious diseases as the result of pathogen mutation and zoonoses. Host susceptibility, is at the peak of the pyramid because that parameter depended on all other factors including changes in environment, socio-behavioral changes and food consumption habits.

The findings provide a guide to policy-makers to identify the impacts of cumulated anthropogenic interference that are resulting in global pandemics. It should help them to strengthen their surveillance strategies to conserve dynamic natural resources to reduce the probability of future pandemics.

6. Sustainability implications

Loss of biodiversity, ecosystem destabilization and climate changes are caused by human overexploitation of nature and natural resources. Environmental regulations are difficult to implement, so are cultural and practical issues associated with industrial farming of livestock's and stopping the wildlife trade. Preserving biodiversity and reducing human-wild inter-connections may help to reduce the incidence of established pathogens, and their re-emergence.

Careful and thoughtful use of wildlife species and their habitats along with stringent rules to restrict wildlife trade is required to avoid not only species extinctions, but also for helping to ensure future human existence, because all species lives depend upon a 'properly functioning eco-sphere on planet Earth!'

7. Discussion: the concept of 'planetary health'

The emerging and re-emerging pandemics have made and are rendering societies helpless repeatedly during many centuries. Although, the epidemic characteristics of pandemic outbreaks have been studied extensively, coupled with million-dollar research and development to control each epidemic as and when it emerged, our societies were not prepared for the global shutdown when COVID-19 lashed the world. This reminded us of the magnitude of the devastating effects of anthropogenic activities.

The extensive destruction of natural habitats for urbanization and modern agriculture have led to biodiversity losses and to extensive species extinction due to habitat loss and destabilized ecosystems. Pollution and carbon footprints coupled with climate changes contributed to global changes in temperatures and emergence of vector-borne diseases. The illegal trade of wildlife and bush meat consumption habits of humans, and extensive industrial farming of livestock fed with antibiotics accelerated the rapid mutations in infectious agents.

Table 6
MICMAC ranks of the causative factors found to be influential in the disease ecology of emerging infectious diseases.

Factor	Driving power	Dependence	Driving power/Dependence	MICMAC rank
F1	3	13	0.231	7
F2	6	10	0.600	5
F3	9	8	1.125	4
F4	14	1	14.000	1
F5	9	8	1.125	4
F6	11	5	2.200	3
F7	6	10	0.600	5
F8	4	11	0.364	6
F9	11	5	2.200	3
F10	12	2	6.000	2
F11	12	2	6.000	2
F12	3	13	0.231	7
F13	1	14	0.071	8
F14	9	8	1.125	4

		Independent zone (IV)							Linkage zone (III)						
Driving Power↑	14	F4													
	13														
	12		F10,F11												
	11					F6,F9									
	10														
	9								F3,F5,F14						
	8														
	7														
	6										F2,F7				
	5														
	4											F8			
	3													F1,F12	
	2														
	1														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
		Autonomous zone (I)							Dependent zone (II)						
		Dependence →													

Fig. 4. MICMAC graph.

The 'adaptive selection' of this genetic changes contributed to the evolution and emergence of pandemic pathogens with high mutation rates, like the Corona-family viruses. The selective mutations may help them to emerge and re-emerge repeatedly in various geographical locations, by passing through multiple host species, adapting to wide ecological niches, and carefully escaping the host's immune system's surveillance as was documented in the genome mutations of SARS-CoV-2.

Human life on earth might have to confront the worst disease syndrome that we can imagine due to the expected ecological backlashes created by nature destruction activities of humans. According to WHO, between 2030 and 2050, about 250,000 deaths per annum will happen due to global warming, malnutrition, climate changes and infectious diseases [142].

Considering the global vulnerability to public health emergencies, to ensure safety and bio-security, international collaborations and partnerships should be enhanced and should encourage preparedness to the next public health crisis. Since, environmental regulations are difficult to implement, surveillance systems with real time tracking, warning and response systems with strict law enforcements are very important to prevent, predict and contain outbreaks with immediate effect.

Emergence of a novel pathogen with epidemic potential is like a volcano eruption bringing out all incubating inner fires at once. By learning from previous pandemics, and their much-discussed causative factors, we should look deeply into the 'inner fires we have created on mother Earth', which has led to the emergence of pandemic diseases. The concept of 'planetary health' has emerged instead of human health, as the repeated lashes of pandemics like COVID-19 challenge us to come out of our attitude of supremacy over other species, and become increasingly be motivated to respect, care for and protect nature and other fellow creatures for the short and long-term future so, generations after generations will also have sustainable futures on this planet!

CRediT authorship contribution statement

S. Lakshmi Priyadarsini: Conceptualization, Data collection, Writing - original draft. **M. Suresh:** Methodology, TISM model construction, Data collection. **Donald Huisingsh:** Conceptualization, Writing - review & editing, Supervision.

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