Imperial Journal of Interdisciplinary Research (IJIR)
Vol-2, Issue-10, 2016
ISSN: 2454-1362, http://www.onlinejournal.in

Major Factors Responsible for Diseases Enhancement: A Review

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Abstract*: This paper reviews studies on diseases enhancing factors in human, in a cumulative manner, with special emphasis on changing environmental conditions due to human activities. In present time growing population is responsible for deforestation, urbanization, and excessive exploitation of natural resources which results into drastically changing environmental conditions. Climatic difference, rising temperature leads to global warming which has substantial adverse effect on human health and we become prone to diseases. Abruptly changing environmental conditions support the persistence of highly infectious diseases like Dengue, Malaria, Chikungunya, Tuberculosis etc. Due to ever changing climate in tropical and subtropical countries new sustainable vector species are flourishing. Apart from horizontal gene transfer (HGT) which spreads genetic diversity by moving genes across species boundaries by rapidly introducing newly evolved genes into existing genomes, adaptability to environment among organisms for their survival and development to resist adverse conditions leads to genetic variability through evolution. Failure to combat the diseases with available different re-sources for therapeutical use, including antibiotics and vaccines is the outcome of the modified genetic makeup of organisms. Genomic variability and novelty has made many infectious organisms to evade immune system efficiently and they are not traceable until reach highly viremic stage. Financial, educational, food, shelter and healthcare inequality among people have worsened the situation and causing more damage to poor rather than affluent people around the world.*

1. INTRODUCTION

Human activities cause global environmental change which affect almost every aspect of life (Fig.1). Scientists have been focusing on effects of global environmental changes including human health and infectious diseases in many reviews [1-6]. Some reviews have also concentrated on vector borne diseases [4, 7- 9]. Two major vector borne diseases such as Dengue and Malaria have been of great concern to us from many decades. “Dengue” a highly endemic vector born viral disease which has crossed the tropical boundaries and threatening the people globally because it causes great human suffering, moreover, no effective antiviral or vaccine is available for its treatment. Dengue is caused by the four serotypes of dengue virus (DENV 1–4) from the *Flaviviridae* family (Flavivirus), and can be found in more than 100 countries distributed through the America, Africa, Southeast Asia and islands from the western Pacific to the eastern Mediterranean. Around two fifths of the world population lives in the areas infested with *Aedes aegypti*, the main vector of dengue viruses [10].

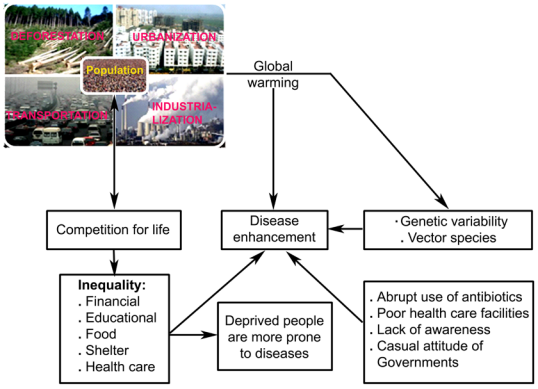

Figure 1. A schematic representation of the disease enhancing factors in human

Malaria also imposes a significant health and economic bur-den in large parts of the world, particularly in sub-Saharan Africa and Southeast Asia [11]. The disease is caused by protozoan parasites of the genus Plasmodium, which are transmitted by female Anopheline mosquitoes. Human malaria can be caused by five Plasmodium species: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. Due to the high mortality and/or morbidity caused by P. falciparum and P. vivax, these species have been given more importance for targeting new strategies and carryout intense research. Most virulent species *P. falciparum* is responsible for the vast majority of deaths in sub-Saharan Africa, primarily of young children and pregnant women.

Among other infectious diseases, tuberculosis is one of the deadliest disease after HIV/AIDS. WHO latest reports claims that in 2013, incidence of people fell ill with TB was 9 million and 1.5 - 2 million dying from the disease worldwide annually. One third of the global population is latently infected with *Mycobacterium tuberculosis* (*M. tb*), which represents a huge pool of hosts at risk of M. tb, reactivation [12]. On the other hand, Non-Communicable diseases (NCDs) including coronary heart disease (CHD), stroke, chronic obstructive pulmonary disease (COPD), cancer, type-2 diabetes mellitus (DM) and chronic kidney disease (CKD) are more prevalent in high income countries (HICs) in comparison to low and middle income countries (LMICs), and currently the leading cause of adult death and disability worldwide [13, 14]. The overall top 10 leading causes of deaths worldwide are represented in the figure 2 [15].

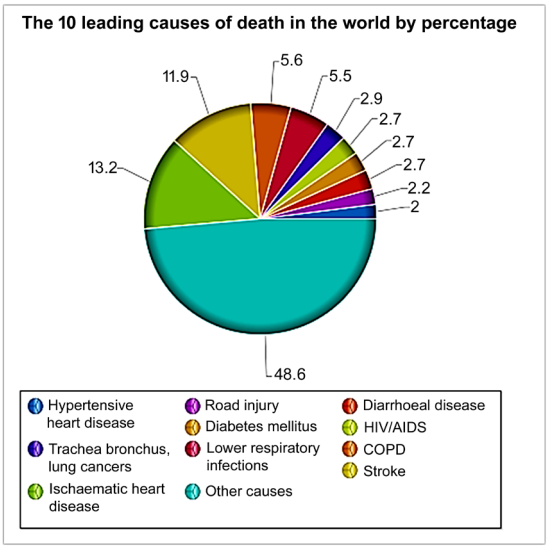

Figure 2. Top ten causes of deaths worldwide (figure adopted from WHO, 2014: www.who.int/mediacentre/factssheets/fs310/en/)

2. FACTORS RESPONSIBLE FOR DISEASES

2.1 Pollution

Pollution hugely affects our health and weakens immunity due to which we become more susceptible to diseases. Our environment is a mix of naturally occurring chemicals and xenobiotics introduced by human activities. Anthropogenic sources produces hazardous air pollutants including mobile sources (cars, trucks, buses etc.), stationary sources (factories, refineries etc.), indoor sources (building materials, cleaning solvents etc.), as well as natural sources (volcanic eruptions, forest fires, fuel combustion etc.).

We generally get expose to extremely complex toxic environmental chemicals (http://www.atsdr.cdc.gov/SPL/index.html).
Hazardous air pollutants (HAPs) also known as air toxics are believed or suspected to cause serious health effects such as cancer, neurological disorder, reproductive, and respiratory problems [16]. Among other air polluting agents, polycyclic aromatic hydrocarbons (PAHs), a group of toxic organic compounds are very harmful for people who are exposed to them. PAHs are mainly generated through incomplete combustion or pyrolysis of carbon-containing materials and are widely distributed in the environment. Long-term exposure to PAHs-rich emissions may lead to cardiopulmonary diseases [17, 18], and lung and skin cancer in exposed workers (http://monographs.iarc.fr/ENG/Monographs/vol92/mono92.pdf.). Particulate matter (PM), especially particles less than 2.5 μm in diameter (PM

2.5), is a key component of biomass fuel smoke. Expo-sure to PM has important effects on the development of respiratory diseases, particularly; it is associated with lung cancer, chronic obstructive pulmonary disease, acute respiratory infections (mainly in children), asthma, and cardiovascular disease [19-24, http://www.atsdr.cdc.gov/SPL/index.html]. Carbon monoxide (CO) is a major component produced by the incomplete combustion of carbon-containing biomass fuels. CO, due to its higher affinity to hemoglobin as compared to oxygen; is a responsible factor for tissue hypoxia thus; carboxyhemoglobin and oxygen saturation levels in the blood are key indicators in determining the effects of acute CO exposure. CO also acts through direct CO-mediated damage at the cellular level [25]. Acute exposure to high levels of CO can cause illness like anemia, asthma, coronary artery disease, which impair tissue oxygenation, and lethal neuropsychiatric disorder [26]. Ernst and Zibrak [27] found that nanoparticles of barium chloride are toxic for colostral mononuclear (MN) phagocytes and also reduce cell viability and release intracellular calcium which increases apoptosis rate. Apart from air pollution, noise is also a pervasive environmental exposure in metropolitan cities. More than one million healthy lives are estimated to be affected annually due to environ-mental noise in Europe, with the largest burdens attributable to sleep disturbance and annoyance [28].

2.2 Genetic variability

Rapidly evolving pathogens creates pressure on the immune system. Immune system must also evolve rapidly to maintain the ability of the host to survive and reproduce. Studies have shown that genetic variability also contributes to spread and sustainability of infectious diseases. Infectious diseases can be regarded as a complex multifactorial disease, with both genetic and environmental variation contributing to differing susceptibilities to infection, and differing effects of infection [29]. In a study based on deep sequencing carried out by Sim et al. it was shown that how DENV diversity can be tracked under different selection pressures, which can come from human or invertebrate hosts or drug treatment [30]. Replication of DENV relies on an RNA polymerase with poor proofreading capabilities. Many variants are formed because of error-prone replication, resulting in a quasi-species [31, 32]. Viral fitness, the replication environment, and other factors determine which mutations become fixed in the viral population. Some studies advocate that optimal mutation rate produces genetic variability while limiting the accumulation of deleterious mutations [33, 34]. Antiviral treatment typically results in the eradication of susceptible variants, however, minor populations of resistant viruses acquire replicative space to expand and this leads to failing of antiviral regimen [35]. The important role of minor subspecies in accelerated resistance has been shown in various viruses, including HIV [36] and hepatitis C virus (HCV) [37]. In the case of HCV and influenza virus, drug-resistant strains arise due to single-nucleotide polymorphisms (SNPs) [38], which are easily acquired due to the error rate of the RNA polymerase. Many resistance genes evolved long ago in natural environments with no anthropogenic influence but these genes are now rapidly spreading among human pathogens. Horizontal gene transfer (HGT) is the movement of genetic information between organisms, a process that includes the spread of antibiotic resistance genes among organisms. Once transferred, the genes and pathogens continue to evolve, often resulting in bacteria with greater resistance [38, 39]. Besides, drug resistance genes, other genes like virulence determinants also get transferred through HGT mechanism and this give an extra advantage to the pathogens [41]. Ongoing HGT poses a problem for clinical surveillance and treatment. Rapid evolvement of population of bacteria results in diversity that necessitates individual screening to determine effective treatments and to detect new strains, such as methicillin and high level vancomycin resistant S. aureus (MRSA and VRSA) [42].

2.3 Vector species

It has been observed in recent years that due to human activities for fulfilling increasing needs, climate change have accelerated the spread of vector-borne diseases even in those areas where they were not present earlier [43-45]. Increasing number of most devastating vector borne human diseases outbreaks are caused by mosquitoes, for example Dengue and Malaria. Malaria is responsible for more than 200 million cases and 2 million deaths every year, while dengue is responsible for ~400 million cases [46-47] and around 500,000 deaths annually, with transmission occurring worldwide, through equatorial, tropical and subtropical areas [48]. Due to changing weather conditions which also includes drought, forcing people to keep water in container sat in their houses. Those reservoirs can be used by anthropophilic and container breeding species such as *Aedes aegypti* (*A. aegypti*) as breeding sites, where they face no predation or competition [49].

The increase in mean temperature and changing sea level interfere with precipitation frequency and some other climatic conditions. These conditions favor

vector reproduction, development rate and longevity [50]. Due to climatic differences, the rainfall pattern changes which affect transmission of diseases by influencing environmental factors, such as vegetation cover, and the availability of associated breeding sites. Insects, capable in transmit-ting disease, migrate to new unaffected places when temperature rises, and start spreading the disease in those areas [51]. The use of climate based density maps is a good correlating tool when matched with the observed disease distribution and weather conditions [52, 53]. From an epidemiological point of view, the increased number of intermittent feedings per replete feeds as consequences of a 2 or 3 degrees increase in temperature is equivalent to a doubling of the density of *A. aegypti* [54]. The relationship between climate and mosquito density is a result of greater availability of breeding sites for mosquitoes that comes with higher rainfall and higher temperature, this increase developmental speed [55]. A study based on West Nile virus (WNV) infection in *Culex pipiens* showed that higher temperature accelerated viral replication in invertebrate hosts, and shortening the incubation periods for a new transmission [43]. Out of five etiologic agents of malarial parasites, four different protozoan species are present in 108 countries and these are transmitted by Anopheles mosquitoes. Africa is the most affected continent hosting ~90% of all malaria deaths [56-58]. Furthermore, there are reports of the re-emergence of other diseases transmitted by mosquitoes, such as encephalitic diseases (St. Louis, Japanese, Venezuela, and West and East Equine Encephalitis) and West Nile disease, which became a major concern in the USA after an epidemic in 1999 [59]. The first major urban out-break of Chikungunya virus (CHIKV) was reported in 1960s in Bangkok, after that another outbreak was announced in 2004, starting from Kenya and spreading over other islands in the Indian Ocean. CHIKV also invaded approximately other eighteen Asian countries and Europe and North America [60].

2.4 Abrupt use of antibiotics

Overuse of antibiotics has become an important factor in the development of antibiotic resistance. Prescription of antibiotics is preferable by physicians because they fear the sin of omission, failure to treat a treatable infection much more than they fear an adverse con-sequence of commission. The perception towards prescription of antibiotic is that they are inherently safe drug, and if there is no infection also, there is little risk in taking an antibiotic. Patient wants quick relief in a timely fashion for a treatable disease and it becomes apparent to everybody including physician and peers. The omission is nearly not excusable. Although, if a patient does not require anti-biotic prescription, and physician still unnecessarily prescribe it, it doesn't matter, if he recovers without knowing ill effect of it. Surprisingly, excess prescription has become tradition in health sector. Conversely, the adverse consequences of drug interaction, replacement of normal flora, direct toxicity, and transfer of resistant organ-isms are often so remote in time that the patient and prescribing physician are unaware that inappropriate prescribing of antibiotics is the root cause. There is commonly an acceptance of these as evidence of the potency of the agents used, even for the immediate adverse con-sequences such as allergic reactions. A physician often prescribes antibiotics for illnesses such as cold, bronchitis, and other infections caused by viruses, which does not respond to the antibiotic drugs [61]. Physicians generally believe that the pre-scribed antibiotics are appropriate in the contexts of their care of individual patients and of their personal clinical practices. A significant proportion of all antibiotics generally prescribed unsuitably in the United States and other countries including Canada, France, England, and the Netherlands [62, 63] although, under prescribing is also an issue there [62]. Menacingly, broad spectrum antibiotics prescription has been increasing now days [64, 65]. This trend towards broad spectrum pre-scribing holds nonetheless of the type of infection or indication for antibiotic treatment making matters worse. Resistance genes that have evolved in one group of bacteria can spread through horizontal gene transfer in intra or intergenic species of bacteria [66]. Due to difficulty in making a reliable and rapid clinical diagnosis, for children infected with influenza, is one of the prime factor leading to inappropriate prescription of antibiotics. Fever and cough are the most common symptoms, but influenza infection can have an anomalous presentation, especially in children, and no single symptom can confirm or exclude influenza [67]. Distinguishing between the clinical features of bacterial infections and influenza is the main challenge for physicians. Most community settings lack the laboratory tests such as complete blood count and C reactive protein measurement which might help recognize bacterial involvement. Reverse transcription polymerase chain reaction and viral culture are the standard criteria for diagnosis of influenza, but both methods require specialized laboratory facilities, moreover, they are expensive and time-consuming [68]. Although, some of the test such as neuraminidase activity or immunoassays can detect influenza A and B viruses within 30 minutes, even though facilities to carry out these test are not available everywhere [69]. In countries, where the climatic changes are abrupt and chances of infectious diseases like dengue, Chikungunya, tuberculosis, and malaria etc. are more, people do not generally take pre-cautions for the treatment of diseases especially in developing

countries. Occasionally, people buy medicine without any prescription from a physician and get wrong medication which makes the condition worse to treat a treatable disease and this also leads in development of antibiotic resistance in microorganisms.

2.5 Financial resources

All people of disease endemic countries are not aware of disease control; they lack knowledge of transmission of diseases, particularly in rural and less developed urban areas. There is huge financial inequality among the people in developing countries due to lack of proper education and unemployment. Hugely populated country's people face more competition and struggle a lot to grab employment opportunities for their livelihood. Generally in less and middle in-come countries, the poor people migrate from villages to urban areas for employment, but there also due to their less paid jobs, they are forced to stay at low cost congested places which lack proper sanitized shelter for their stay. Moreover, unavailability of proper food, families of poor people suffer from malnutrition and this weakens their immunity. Due to unequal living standard, poor people are more prone to disease transmission rather than affluent people because they hardly earn adequate money for their survival and have no money for healthcare. If they are diagnosed with disease properly then also good healthcare facilities are away from their reach because healthcare cost seems to be sky touching for them. On the other hand, the governments of diseases endemic countries do not have sufficient financial resources, due to which, health workers in the public sector are often overworked and underpaid. They lack proper supervision, training, equipment, and drugs. Often, the local population is dependent on public health sector facilities, where they are not treated well. Conversely, the private sector faces their own problems and due to lack of regulatory measures the situation gets worse as they are not enforced by the health system properly. Unlicensed private medical practitioners provide costly and inappropriate prescription without having enough knowledge about the diseases. Correcting these situations is a tremendous challenge that must be ad-dressed if disease control and ultimately elimination is to be successful.

Maximum deaths (~68%) occur due to non-communicable diseases worldwide (WHO, 2014). However, in low and lower-middle income countries people mainly suffer from infectious dis-eases, which is a major cause of people's death there. According to WHO (2014) report, which is based on different income criteria of low, lower middle , upper middle and high income countries the deaths occurred in year 2012 are shown in figure 3.

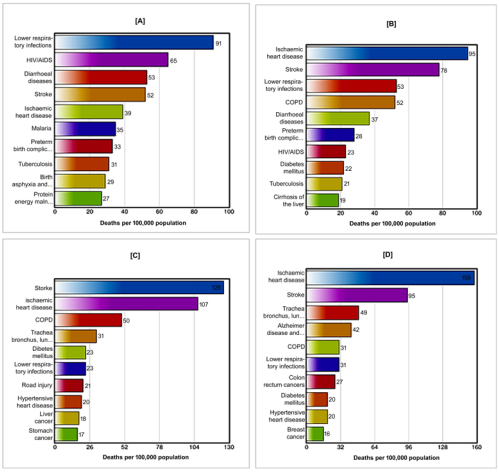

Figure 3. Causes of deaths in year 2012. (A) Top 10 causes of death in low-income countries, (B) Top 10 causes of death in lower-middle income countries, (C) Top 10 causes of death in upper-middle countries, (D) Top 10 causes of death in high income countries. Data adopted from WHO report, 2014 (www.who.int/mediacentre/factssheets/fs310/en/)

3. WHAT CAN BE DONE?

The above discussed factors are responsible for progression of dis-eases in a cumulative manner. There is tremendous need of collective efforts made by all, ranging from individualistic responsibility to making the public aware by the government of the affected countries, to minimize the severity of diseases in a particular area. Use of public transport should be encouraged, if the air and sound pollution is to be minimized and to reduce congestion on the roads which minimizes the burning of fuel by vehicles in idle condition. It will also save money and support healthy living. Burning of polythene, plastic, rubber, plant remains, and house hold waste should be banned. Eco-friendly fuel should be used for running the vehicles and use of diesel must be allowed for agriculture or unavoidable goods transportation purposes only rather than using it for running private vehicles. Regulatory bodies should enforce the law strictly and monitor the mixing of wastes arises from industries to water bodies and only be released after proper removal of contaminants which are harmful for flora and fauna present in water. During the transient stage of weather, health care department should get ready for controlling the spread of diseases and making the public aware to maintain hygiene and to save them from mosquito bite to avoid the infection. Government hospitals should be made enabled with the equipments, drugs, and proper training to act in

every possible condition of emergency. Health workers should be willing to learn new things about the treatment of patients infected with new emerging diseases and update their knowledge regularly. Careful prescription should be made when comes to use of antibiotics. General public should avoid using antibiotics without proper prescription. Physical activity should be included in daily routine to live a healthy life and to avoid disease infection. Government should make arrangements to fulfill basic needs of the citizens such as food, shelter, and healthcare to avoid migration of the people from rural areas to urban areas. People should take nutritive food to maintain their health. Private and non-government organizations (NGOs) should work together with government in providing the information about the area where children suffer from malnutrition. Private and public sectors should take initiatives to educate people and also donate money for the common cause of betterment of people's life in developing countries. Re-search in the area of health care and bio-energy generation in developing countries should be encouraged.

4. CONCLUSION

Growth compliments evolution which is a natural phenomenon and should not be hindered at any cost in rapidly changing environment with the advancement of technology in highly competitive world. It is obvious that, we may not control emerging needs for our survival but our systematic and disciplined action can make us to live long and keep away from harmful effects which we face due to our casual attitude towards our environment. Suffering from diseases or any other causes can be reduced to large extent if cannot be eradicated completely also, by spreading every kind of knowledge for the betterment of coming progenies.

ACKNOWLEDGEMENTS

SK was supported by the Department of Biotechnology Government of India, (Grant no. BT/PR4092/MED/29/338/ 2011 and BT/PR7427/BRB/10/1178/ 2013). AK was supported by National Postdoctoral Fellowship funded by Science & Engineering Research Board, Govt. of India [Award No. PDF/2015/000474]. DB was supported by Council of Scientific and Industrial Research-Pool officer Fellowship, Government of India.

COMPETING INTERESTS

No competing interest.

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