

Review Article

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## Pandemic of Infectious Diseases due to New Etiological Agents Predisposing Factors, Case study of COVID19 and Control Measures

Neha Pant and R. S. Chauhan\*

Department of Pathology, College of Veterinary and Animal Sciences  
G B Pant University of Agri. & Tech. Pantnagar-263145 Uttarakhand, India

\*Corresponding author

### ABSTRACT

Today the whole world is in an endeavor to deal with a newly arrived pandemic, COVID-19 which has all the potential to be catastrophic to mankind at its worst. This is not new; the world faced many pandemics earlier. According to the WHO, the worldwide spread of a new disease is called a pandemic that is if an infection becomes widespread in several countries at the same time, it may turn into a pandemic. Pandemic may be a result of new infection resulting from the evolution or change of an existing pathogen/parasite resulting in a change of host range, vector, pathogenicity or strain; or the occurrence of a previously unrecognised infection or disease or due to a known or endemic disease that either shifts its geographical setting or expands its host range, or significantly increases its prevalence. Whenever a new bacterial or viral strain is formed or the existing ones undergoes genetic variation due to mutation like genetic shift, genetic drift or genetic reassortment and have a capability of rapid transmission and infecting large population then they have a potential to cause pandemic. Man has constantly altered its ecosystem by its activities. Tracing of the origins of emerging infectious diseases back to first emergence in the human population, lead to the revelation of some distinctive patterns. There are a number of agents present in the environment to which our body is exposed all the time. Not everyone exposed to these agents develops disease. Immunity is a major factor that governs susceptibility of individual towards any disease and thus governs health. People with low immunity are very susceptible to any disease and even a mild disease can take severe form in such individuals while people with strong immune system are comparatively resistant to infection. In today's scenario, the lifestyle of people is exposing them to various chemicals in a way that now chemicals are part and partial of our life, be it flavoring agents, food colours, skin lotions, cleansers, disinfectants, fertilizers, pesticides, medicines, washing powder or soaps etc. Many of these chemicals either singly or in combination are proved to be a major cause behind the decreased immunity of people now days. As people around the globe are exposed to such chemicals around the clock hence it may be a major cause of mass immunosuppression. Due to which population immunity goes down and the resistance towards coming infection decreases hence they become susceptible to coming infection. This may be a major cause of an endemic disease firstly becoming epidemic then pandemic as well as a possible reason behind progression of any novel infection within the population. Being too clean might be making us sick due to development of immunologically virgin population. Even the obsessive washing of hands and excessive hygienic measures because may result in developing immunologically virgin population which is not exposed to the environment. For containment of any pandemic an amalgamation of rapid diagnosis, prevention and control, case management i.e. treatment and mass vaccination is required. Because of their changing antigenic type vaccine development is strenuous job. Additionally, it has been proved now beyond any doubt that the allopathic system of medicine alone may not be able to control any such pandemic or epidemic. It includes ayurveda which gives prime importance to prophylaxis. Ayurveda have several strong points in preventive care like scope of prevention is very large, no or very minimum side or after ill effects are seen. It also includes cowpathy which is an age old system of medicine described in ancient Indian literature and also known as 'Panchgavya Chikitsa'. In order to reduce the immunodeficiency, some of the nutrients like vitamins, roughages, antioxidants, lipids, Carbohydrates, Proteins, Ionophores, Carotenoids, Bioflavenoids, Omega-3 fatty acids, etc. and crude preparations of some microorganisms are also used which are necessary for the development of the body to improve the nonspecific and specific immunity. There is a need to explore novel therapeutic approach like convalescent plasma treatment which has been shown to be effective in treatment of COVID-19, swine influenza, SARS etc. The pandemics we have experienced so far have shown a number of deficiencies and defects, including vulnerabilities in global, national, and local public health capacities; difficulties in decision making under conditions of uncertainty; limitations of scientific knowledge; complexities in international cooperation; and challenges in communication among experts, policymakers, and the public. Pandemics can be contained only by an amalgamation of rapid diagnosis, prevention, control, case management and mass vaccination. Global surveillance of emerging and previously unknown infections in both human beings and other species should be done. Preparation beyond planning, with advance protocols and agreements, the commitment of ready reserves of public health experts and a financial line of credit, and the fulfillment of the international health regulation requirements can all help. Besides, the known therapeutic and preventive measures in our own traditional system and are proven on the standards of the modern scientific parameters must be used instantly without any doubt and wasting time in further research in order to save the population at large and minimize their sufferings.

### Keywords

Pandemics,  
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## Introduction

Today the whole world is in an endeavor to deal with a newly arrived pandemic, COVID-19 which has all the potential to be catastrophic to mankind at its worst. This is not new, the earliest recorded pandemic happened during the Peloponnesian war in 430 B.C., known as the plague of Athens. After that the world faced many pandemics one after the other. some of the major pandemics that have occurred over time are namely Antonine Plague in 165 A.D.; Cyprian Plague in 250 A.D.; Justinian Plague in 541 A.D.; Leprosy in 11th Century; The Black Death in 1347-1351; The Great Plague of London in 1665; Cholera Pandemics 1-6, 1817-1923; Fiji Measles Pandemic in 1875; Russian Flu in 1889-90; Spanish Flu in 1918-19; Asian flu in 1957-58; Hong Kong Flu, 1968-1970 HIV/AIDS in 1981-present; SARS in 2003; Swine Flu, 2009-2010 and Covid-19, 19-present (Clendening, 1960; Porter, 2010).

According to the WHO, the worldwide spread of a new disease is called a pandemic. If an infection becomes widespread in several countries at the same time, it may turn into a pandemic (WHO;2010). There are a number of agents present in the environment to which our body is exposed all the time. Some of them are highly pathogenic causing severe illnesses, some are moderately pathogenic causing moderately severe illnesses, some are less pathogenic causing mild illnesses and most of them are believed to be non-pathogenic that does not cause any illness at all. Not everyone exposed to these agents develops disease. For example- not everyone exposed to beta-hemolytic streptococci develops acute rheumatic fever (Park, 2011). However, in an undernourished or otherwise susceptible person may result in clinical disease. Majority of bacteria and viruses are opportunistic pathogens which mean they are natural inhabitant of body and does not cause

any disease in people having good immunity but as the immunity goes down they cause disease (Quinn *et al.*, 2011). So, immunity is a major factor that governs susceptibility of individual towards any disease and thus governs health. People with low immunity are very susceptible to any disease and even a mild disease can take severe form in such individuals (Baveja, 2005; Chauhan, 2018). Comorbidities are common in individual with low immunity. For example- HIV virus causes immunosuppression in the people which make them highly susceptible for other infections, even simple infection can take form of complex disease in patients with HIV-AIDS (Chu and Selwyn, 2011; Shen, 2016). In contrast, people with strong immunity are less susceptible for infections and suffer less with diseases (Benenson, 1981; Owen *et al.*, 2013). In today's world, the lifestyle of people is exposing them to various chemicals in a way that now chemicals are part and partial of our life making them immuno compromised. Pandemics cause huge economic losses as well as losses in terms of human morbidity and mortality.

In the thirst of modernization and industrialization man has contributed pollution to the life and ecology of plants, animals and microbes. Increased demand for food and fiber has lead to the chemicalisation of agriculture and we have reached on such a stage that modern agriculture is dependent on high yielding varieties, which can only be grown under the influence of fertilizers and pesticides. Pesticides are the manmade chemicals which are being used to produce enough cheap food. In India, 2,16,703 MT of technical grade pesticides are produced during 2018-2019 to control pests and plant diseases. The pesticides are classified as insecticides, fungicides, weedicides, rodenticides, plant growth promoter and biopesticides (Chauhan, 2020).

Majority of these pesticides are beneficial when used for specific purposes, handled properly and applied as per the recommendations of the manufacturer. However, over the years, there has been a mounting fear and concern that indiscriminate and disproportionate use of pesticides may lead to their residues in food chain which may exert their harmful effects in human beings and animals. In an ideal pesticide application, the chemical should fall exactly on the target and be degraded completely to harmless compounds but this never occurs and only some part of the pesticide hits the target pests while remaining drifts into the environment (Banga *et al.*, 2005; Chauhan, 2017).

If we look retrospectively, we find that the use of pesticides started during Second World War when these hazardous and toxic poisons were considered as chemical weapons. A Swiss scientist Paul Muller invented DDT in the year 1939 which was considered as a wonder chemical that kills the insects, pests and was found wonderful in malaria control programmes. But soon after the discovery of DDT, its harmful effects also came into the knowledge of the scientists. In 1944, A famous biologist found harmful effects of DDT in birds, which produced thin shelled eggs, easily broken in nests resulting into failure of reproduction and decline of bird population.

The amount of pesticides used in India is very low (only 0.5 kg/ha) as compared to other developed countries, even then we have much higher pesticide residues in food of our country. There is a gradual increase in production and consumption of pesticides during last few decades. The pesticides consumption increased from 2353 MT during 1955 to 48,743.55 MT (technical grade) in the year 2018-2019 (Chauhan, 2020). About 20% of Indian food products contain pesticide residues above tolerance level compared to

only 2% globally. No detectable residues are found in 49% Indian food products compared to 80% globally. It is all because of following reasons which needs to be looked in order to reduce the level of pesticide residues in animal products and other food material below MRL value. Man is the ultimate consumer of pesticide residues. Through fodder, water, air and other feed stuffs pesticide residues reaches in animals and then through milk, meat, egg and other animal products accumulates in human being. Various pesticide residues have been reported from animal products in our country important among them are DDT, Carbaryl, Hepatochlor, PCB etc. These pesticide residues in animal products and other food items ultimately get accumulated in the man especially in the adipose tissue, blood and lymphoid organs. Most of research on pesticide toxicity has been directed towards the assessment of their acute effects. When fed to man or animals at very low doses daily for months or years, these accumulated pesticides in body, may harm the normal functions causing various diseases in man and animals (Chauhan *et al.*, 2001; Chauhan and Tripathi, 2002).

The presence of pesticide residues have been detected in various items and in food chain. The levels of the pesticides are found much higher than expected level because of heavy contamination of environment. A list of commodities is given in which very significant levels of pesticides are recorded. Besides, there are human milk, fat or tissue samples screened for the presence of pesticide residues were also found to have very significant levels of harmful pesticides. The BHC has been found from 0.120 to 1.22 PPM in human fat samples. Heptachlor, an organochlorine pesticide was found to be 0.425 PPM and DDT from 0.195 to 1.695 PPM. Even human breast milk is not free from DDT, which was found to have even

2.39 PPM levels. Similarly human blood was found to have a much higher concentration of 12.00 PPM as against of 0.050-PPM safe levels (no observable effect levels) (Chauhan and Singh, 2001).

Disease is rooted in the ecosystem of man. According to ecological concepts, health is envisaged as a state of dynamic equilibrium between man and his environment. Man has constantly altered its environment or ecosystem by activities as deforestation, industrialization, urbanization, land reclamation, construction of dams and irrigation canals, and has created new health problems for himself. For example, in today's scenario the greatest threat to human health is the unplanned and ever-increasing urbanization, growth of slums and deterioration of environment which has resulted in increasing dimensions of the diseases i.e., diseases which once thought to be primarily "rural" (e.g., filariasis) have now acquired serious urban dimensions. There is re-emergence of several diseases. Agents of several diseases, for example, chikungunya fever and malaria, which were effectively controlled once, have shown a recrudescence. The reasons for this must be searched in terms of changes in the human ecology. Man's intrusion into ecological cycles of disease has resulted in emergence of zoonotic diseases such as Kyasanur forest disease, yellow fever, rabies, Lassa fever, etc. Even the Bhopal gas tragedy in 1984 highlights the danger of locating industries in urban areas. Construction of irrigation canals and artificial lakes has favoured the breeding of mosquitoes and snails by creating ecological niches for them (Park, 2011). And most of these act as a vector in various vector borne diseases we are facing today, for example- Female Anopheles mosquito act as a vector for malaria, Aedes mosquito can spread dengue fever, chikungunya, yellow fever, Zika fever and other disease agents.

Tracing of the origins of emerging infectious diseases back to first emergence in the human population, lead to the revelation of some distinctive patterns. The emergence of all major groups of emerging infectious diseases correlates strongly with human population density, supporting the hypothesis that disease emergence is driven largely by anthropogenic changes, such as the, industrialization, urbanization, expansion of agriculture, trades, travel routes, and changes in land use (Weiss and McMichael, 2004).

According to a five stage model proposed by Wolfe and colleagues called pathogen pyramid, emergence of pandemic zoonotic diseases occurs in five stages, out of which in stage two also called localized emergence, initial spillover of a wildlife or livestock pathogen to people occur (Wolfe *et al.*, 2007). It may be caused due to handling of butchered wildlife to exposure to fomites in wildlife markets or livestock farms, or in the wild. The outcomes vary widely, from small clusters of human cases (eg, Menangle virus) to large outbreaks, some with limited person-to-person transmission (eg, Ebola virus) and some without person-to-person transmission (eg, Hendra virus) (Morse *et al.*, 2012). Exposure of human to pathogen can also occur due to its food habit.

For example, COVID-19 is considered to be originated in sea food market in Wuhan where a wide range of wild animals like bats, snakes, poultry are sold and consumed (Lake, 2020). Bats are considered as the source of origin of SARS-CoV-2 virus (WHO, 2020) as well as SARS-like coronaviruses of bats, emerged in China in 2003 which caused SARS outbreak occurred due to hunting and trading of bats for Food (Li, 2005). In the wildlife markets of southern China these bats are sold and consumed, it is said that from bats virus spilled over to civets before being transmitted to people (Guan *et al.*, 2003).

SARS coronavirus then underwent repeated cycles of transmission in people, and spread nationally and then globally. Indeed, ecological factors are the underlying cause behind the geographic distribution of disease. Therefore it has been said that good public health is basically good ecology (Park, 2011). The depletion of ozone layer caused by halogens released due to human activities is not only responsible for increase in exposure of people to highly dangerous UV rays contributing to skin cancer development but is also responsible for immunosuppression contributing to diminished host resistance to infectious diseases.

Immunosuppression may occur either locally in the skin exposed to sun or systematically, at non-exposed sites. In a study, it was shown that irradiation of the skin with UV induce DNA damage which triggers a cascade of immunological events, including decreased antigen-presenting activity, induction of regulatory T-cell activity, as well as causes release of the cytokine IL-10 and other immune mediators out of which, IL-10 essentially decreases delayed hypersensitivity responses, leaving humoral responses undiminished (Mosmann *et al.*, 1991). It leads to a state of antigen-specific, systemic T lymphocyte-mediated immunosuppression.

Thus as a result, suppression of antigen-specific adaptive immunity occurs both locally (at the site of immunological challenge) and systemically (Kripke, 1994; Longstreth *et al.*, 1995). It was proposed that UVR-induced immunosuppression functions maximal at low latitudes and attenuates the autoimmune process that underlies multiple sclerosis. The attenuation could be a result of either diminution in the initial sensitization of T-cells to a newly encountered viral antigen, or a reduced intensity of cell-mediated immune response to ongoing infection with the virus (McMichael and Hall, 1997).

## **Pandemic v/s Epidemic**

According to the WHO, the worldwide spread of a new disease is called a pandemic. A pandemic spreads beyond national borders, covering adjacent countries and possibly worldwide while an epidemic remains limited to one city, region, or country. Generally at first, pandemics are classified as epidemics, which is the rapid spread of a disease across a particular region or regions. For example- COVID-19 began as an epidemic in China, before making its way around the world in a matter of months and becoming a pandemic (WHO, 2020). But it's not always a fast or clear transition between epidemics and pandemics, not always epidemics become pandemics, and it's not always a fast or clear transition. Authorities consider a disease to be an epidemic when the number of people with the infection is higher than the forecast number within a specific region and if an infection crosses the national borders and widespread in several countries at the same time, it may turn into a pandemic. Authorities consider a disease to be an epidemic when the number of people with the infection is higher than the forecast number within a specific region and if an infection becomes widespread in several countries at the same time, it may turn into a pandemic (Gelman, 1970; Last, 2001; WHO, 2010).

## **Why does pandemic occur?**

Pandemic can be caused by a new virus strain or subtype that easily transmits between humans. Antibiotic resistant bacteria may also be behind the rapid spread. Sometimes, pandemics occur once new diseases develop the potential to spread rapidly like the Black Death, also known as bubonic plague. Since against a new virus, humans may have little or no immunity, hence disease progression occurs rapidly. Often, a novel virus cannot spread between animals and people.

However, if the disease mutates or changes, it may start to spread easily, and may result into a pandemic. For example- seasonal influenza (flu) epidemics generally occur as a result of subtypes of a virus that is already circulating among people. Novel subtypes, on the other hand, generally cause pandemics (Last *et al.*, 2001). These novel subtypes will not previously have propagated among humans. A pandemic affects a higher number of people and it can also lead to more social disruption, economic loss, and general hardship on a wider scale. Pandemic may be a result of new infection resulting from the evolution or change of an existing pathogen/parasite resulting in a change of host range, vector, pathogenicity or strain; or the occurrence of a previously unrecognised infection or disease or due to a known or endemic disease that either shifts its geographical setting or expands its host range, or significantly increases its prevalence. Whenever a new bacterial or viral strain is formed or the existing ones undergoes genetic variation due to mutation like genetic shift, genetic drift or genetic reassortment and have a capability of rapid transmission and infecting large population then they have a potential to cause pandemic. Like influenza virus, influenza viruses undergo genetic variation and keep changing their antigenic structure due to which immune system is unable to recognize and fight against them (Quinn *et al.*, 2011). Pathogens can be transferred from human beings to animals and before being transferred back to people, it can be transferred in between different animal species allowing remixing and evolution with potentially enhanced pathogenicity, for example-influenza (Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, 2009; Barber *et al.*, 2011). Memory cells are of no longer use in such situations. Due to their ability of changing their antigenic structure, vaccination is usually not successful in prevention and control of such disease

because the virus or bacteria keeps changing its antigenic structure (WHO, 2009; Kelly, 2011). Hence, pandemic is of global public health concern (WHO, 2020).

### **Immunodeficiency as a leading cause of pandemic**

To understand the correlation between occurrence of pandemic and immunodeficiency in population we need to understand how the disease occurs and what role does the immunity play in disease control. Since time immemorial, man has been involved in trying to control disease. The priest, the herbalist and the medicine man, all undertook in various ways to bring relief to the sick and/or to cure man's disease. Occurrence of any disease is multi-factorial (MacMahon and Pugh, 1970). These factors are determinants of disease. Determinant is any factor that produces a change in the characteristics or frequency of disease when altered. Example: Diet is a determinant of scurvy. Knowledge of determinants helps in the identification of categories of people that are at particular risk of developing disease. Therefore, it is essential for disease prevention as well as it serve as an aid to differential diagnosis. Determinants are described as, Primary and secondary determinants or intrinsic and extrinsic determinants. Primary determinants are the necessary causes whose variations exert a major effect in inducing diseases. Example: - Exposure of human to HIV virus is the primary determinant of AIDS. While, secondary determinants are determinants correspond to predisposing, enabling and reinforcing factors. Example: Monsoon season favours clostridial infections. It is seen that some determinants both primary and secondary are internal to the host and are called intrinsic determinants. Examples: Species, breed, genetic constitution and sex. In contrast some determinants are external to

the host and are called extrinsic determinants for example, transportation, which may result in physical trauma (Park, 2011).

According to advanced model of the triangle of epidemiology, determinants are associated with host, agent and environment. These three factors are grouped together as "epidemiological triad". Other than agent, there are some factors relating to the host and environment which are equally important to determine whether or not disease will occur in the exposed host. For example, it is well-known that everyone exposed to tuberculosis does not develop tuberculosis. The same exposure, however, in an undernourished or otherwise susceptible person may result in clinical disease (Merrill, 2015). In an epidemiological triad, agents of infectious diseases include bacteria, viruses, parasites, fungi, and molds. Regarding non-infectious disease, disability, injury, or death, agents can include chemicals from dietary foods, tobacco smoke, solvents, radiation or heat, nutritional deficiencies, or other substances, such as poison. One or several agents may contribute to an illness. A host offers subsistence and lodging for a pathogen and may or may not develop the disease. The effect that a disease causing organism will have on host is determined by the level of exposure, level of immunity, state of health, genetic makeup and overall fitness of the host. The makeup of the host and the ability of the pathogen to accept the new environment can also be a determining factor because some pathogens thrive only under limited ideal conditions. For example, many infectious disease agents can exist only in a limited temperature range. Environment can be internal i.e. within a host or external i.e. in the community. Finally, time includes severity of illness in relation to how long a person is infected or until the condition causes death or passes the threshold of danger towards recovery.

Epidemiologist is concerned with delays in time from infection to when symptoms develop, duration of illness, and threshold of an epidemic in a population (Park, 2005).

### **Occurrence of disease**

The occurrence of disease occurs in two phases. These are period of pre-pathogenesis and period of pathogenesis. Pre-pathogenesis phase refers to the period preliminary to the onset of disease in man. In this phase the disease agent has not yet entered man, but the factors which favor its interaction with the human host already exist in the environment. This situation is usually mentioned as man exposed to the risk of disease. Likely we are all in the pre-pathogenesis phase of various communicable and non-communicable diseases. Disease in man cannot be started by mere presence of all the three factors of epidemiological triad in the pre-pathogenesis period. Rather to initiate the disease process in man an interaction of these three factors is required.

The agent, host and environment interaction in combination determines the onset of disease which may range from a single case to epidemics as well as the distribution of disease in the community. The pathogenesis phase starts with the entry of the disease "agent" in the susceptible human host. The further events are essentially clear-cut in infectious diseases, i.e., the disease agent then multiplies and induces tissue and physiological changes, progression of disease occurs through a period of incubation and later through early and late pathogenesis. Recovery, disability/death is the only possible final outcome of the disease. The pathogenesis phase may be modified by intervention measures such as immunization and chemotherapy. At this stage, we cannot predict the host's reaction to infection with a disease agent.

That is, the infection may be typical or atypical; clinical or subclinical; or the host may become a carrier with or without having developed clinical disease as in the case of diphtheria and hepatitis B (Paul, 1958; Park, 2011). So by limiting the disease progression in pre-pathogenesis phase we can prevent the occurrence of disease. Primary level of prevention is used. The methods of interventions used are health promotion and specific protection. Primary prevention is removing the possibility that a disease will ever occur by taking action prior to the onset of disease. It is a "holistic" approach. It relies on measures designed to promote health or to protect against specific disease "agents" and hazards in the environment (Park, 2011).

### **Immunodeficiency- decreased resistance and increased susceptibility to infection**

Immunity is the resistance of our body against any foreign antigen. Impaired immune response leads to repeated microbial infections and sometimes enhanced susceptibility to malignancies. Such defects may be primary or secondary. Primary immunodeficiency results from abnormalities in the development of immune mechanisms. Secondary immunodeficiency is due to consequences of some other disease, malnutrition, drugs and other processes that affect the normal functioning of the mature immune system (Baveja, 2005). These immunodeficiency diseases may involve specific immune functions- humoral immunity, cell mediated immunity or both-or nonspecific mechanisms such as phagocytosis and complement. Hence, decrease in resistance of body makes the body more susceptible towards infection. Due to impaired mechanism, repeated infections and comorbidities are common, even a simple disease may take complex form and it becomes difficult to recover from a disease (Benenson, 1981).

The occurrence of disease can be prevented by stopping the progression of disease from pre-pathogenesis phase to pathogenesis phase by primary prevention which essentially involves strengthening immune system hence impaired mechanisms of the host immune system may lead to progression of disease from pre-pathogenesis phase to pathogenesis phase. In people with immunodeficiency there is decreased resistance and increased susceptibility to infection (Benenson, 1981). In today's scenario, the lifestyle of people is exposing them to various chemicals in a way that now chemicals are part and partial of our life, be it flavoring agents, food colours, skin lotions, cleansers, disinfectants, fertilizers, pesticides, medicines, washing powder or soaps etc.

### **Immunodeficiency related to environmental pollutants**

Many pesticides affect the human immune system in ways that suppress the normal immune response of the body towards invading bacteria, viruses, parasites and tumors. The risks are much greater in the developing world. In the developing countries, larger fraction of people works on farm and lives along the countryside. Because in developing nations, pesticide use is still growing rapidly, therefore, people in these countries are more exposed to chemicals. On the top of other health risks, pesticide related immunosuppression might be significantly increasing the burden of diseases. Among the organochlorines, aldrin, dieldrin, lindane, BHC are found to effect macrophage activity, while DDT has been found to produce dose-dependent reduction in antibodies formation. Among organophosphorus and carbamates, malathion is found to dis-regulate immune system by non-specific mechanisms. However, chronic long exposure may interfere with humoral response (Bhatia and Kaur, 1993; Repetto and Baliga, 1997).

The primary concern of the chronic low dose toxicity in man and animals is related to the carcinogenic, teratogenic, mutagenic, immune-toxic, immuno pathological and/or neuropathic effects of pesticides. The perusal of literature in this regard reveals the studies directed towards only one or two pesticides while in nature, when a large number of pesticides are present and their combined effect has not been measured; which of course will give very dangerous view. Most of the pesticides studied during last two decades are found to exert immunosuppressive effect on both the wings of immune system i.e. humoral and CMI. Organochlorines, organophosphates, carbamates and synthetic pyrethroid pesticides were found immunotoxic at “no adverse effect dose” levels in poultry, sheep, and in bovine calves. However, the organochlorines are comparatively much more harmful to immune system. They are considered to be the cause of vaccinal failures or occurrence of disease epidemics in animals due to lowered immuno competence.

It has also been reported that a state of immunosuppression for a longer period may also lead to the development of neoplasms as the immune surveillance mechanism becomes defective. Such animals also exhibit recurrent bacterial infections due to defective phagocytic machinery of the body. Immunosuppressive state of animal for a longer duration may also lead to development of cancers in the absence or defective immune surveillance in body. Since the pesticides affect specific as well as paraspecific immune system adversely, the immune surveillance in body becomes defective. Though, there is no direct correlation but for an example, there is an increased incidence of eye cancer (squamous cell carcinoma of eye) in cattle and buffaloes in western UP during last few years. Similarly the occurrence of canine venereal tumours also increased in dogs

during last decade. It is an indication of the adverse effects of polluted environment and may be related with a state of immunosuppression (Chauhan, 2018). Exposure to heavy metals has a potential of disrupting body's immune homeostasis either by directly acting on the cells of immune system or by acting calls of other organ and rendering them immunologically reactive. Host resistance to variety of pathogens is reduced in metal exposed individual. Lead causes alteration in macrophage activity while Cadmium causes reduction in colony-forming cells within the bone marrow. Similarly mercury and nickel are found to decrease macrophage activity. Hence, by lowering the resistance of body they increase possibility of occurrence of disease (Kowoleko *et al.*, 1992; Chauhan and Agrawal, 1999).

Fumonisin B<sub>1</sub> (FB<sub>1</sub>) is one type of mycotoxins, produced by the fungus *Fusarium verticillioides*, which commonly infects corn and other crops and upon consumption via FB<sub>1</sub>-contaminated food is harmful to human health. In a study, it was found that FB<sub>1</sub> reversed the morphological changes and enhanced the endocytosis of FITC-dextran in LPS-treated bone marrow-derived dendritic cells (BMDCs). Simultaneously, FB<sub>1</sub> decreased the LPS-induced expressions of MHC II, CD86 and CD80 molecules in BMDCs (p<0.05), as well as the T-cell stimulatory capacity of BMDCs (p<0.01). Additionally, the secretions of IL-6, IL-10 and IL-12 were suppressed by FB<sub>1</sub> in a dose dependent manner (p<0.01). The immunosuppressive effects of FB<sub>1</sub> were mainly caused by changing the morphology and interfering with the process of antigen uptake, processing and presentation. The study supported the fact that FB<sub>1</sub> has the capacity to modulate the immune responses of BMDCs (Li *et al.*, 2017). Deoxynivalenol (DON) is one of several mycotoxins produced by certain *Fusarium* species that frequently

infect corn, wheat, oats, barley, rice, and other grains. In a study, it is shown that DON (0.5-10  $\mu$ M) altered three main functions of pig PMNs: LPS-induced secretion of IL-8, chemotaxis, and phagocytosis capability. This alteration of PMN properties was due to apoptosis induced by DON exposure.

It was shown that the effect of DON was mediated by the phosphorylation of the p38 mitogen-activated protein kinase within the first 30 min of exposure. It is suggested that these immunosuppressive effects of DON may have implications for humans when eating contaminated food (Darsanaki *et al.*, 2015). Aflatoxicosis may also cause cancer in man and animals as single etiology or in combination with other agents like hepatitis virus (Chauhan and Dhama, 2008).

### **Immunodeficiency related to chemicals**

Aspartame is most commonly used artificial sweetener found in low calorie beverages, desserts and table top sweeteners added to tea or coffee. It is widely consumed by humans who are diabetic and who are under weight loss regime. Aspartame is rapidly and completely metabolized in humans to phenylalanine (50%), aspartic acid (40%) and methanol (10%). In a study it was revealed that administration of aspartame (40 mg/kg.bw) alters the neutrophil function and humoral immunity as well causes oxidative stress by altering the oxidant/antioxidant balance in blood cells (Arbind *et al.*, 2014).

Sodium benzoate (SB) is a permitted food preservative which is widely used due to its bacteriostatic and fungistatic properties. It is immunosuppressive. The acceptable daily intake of sodium benzoate is 5 mg/kg-BW, however, in the food commodities it has been found to be used at relatively high levels (2119 mg/kg).

In a study, 2500  $\mu$ g/ml dose was shown to be cytotoxic for splenocytes. At 1000  $\mu$ g/ml dose, sodium benzoate remarkably suppresses the proliferation of Con A and LPS stimulated splenocytes at 72 h, while after 96 h, the allogenic response of T cells decreases significantly. It down-regulates the relative expression of CD8 co-receptor.

Further, exposure of splenocytes to sodium benzoate for 72 h causes reduced expression of CD28 and CD95, which play a vital role in T cell activation. It also suppresses the relative expression of CD19, CD40 and CD95 receptors on B cells after 72 h. In addition to the functional responses, it lowers the expression of IL4, IL6, IFN $\gamma$  and IL17 cytokines in Con A stimulated splenocytes; and IL6, IFN $\gamma$  and TNF $\alpha$  in LPS stimulated splenocytes following 48 h of exposure (Yadav *et al.*, 2016).

In this way, most of the substances to which people are exposed today be it environment pollutants or artificial sweeteners or preservative, most of them exert an immunosuppressive effect in them. Several drugs like corticosteroid which are commonly used are also immunosuppressive. Many of these chemicals either singly or in combination are proved to be a major cause behind the decreased immunity of people now days. As people around the globe are exposed to such chemicals around the clock hence it may be a major cause of mass immunosuppression.

Due to which population immunity goes down and the resistance towards coming infection decreases hence they become susceptible to coming infection. This may be a major cause of an endemic disease firstly becoming epidemic then pandemic as well as a possible reason behind progression of any novel infection within the population.

## Over hygiene and immunologically virgin population

Being too clean might be making us sick due to development of immunologically virgin population. We live in an age of cleanliness. Our soaps are antibacterial. The household cleaners we use promise to kill 99.9% of germs. But concurrently, some scientists also tell us that being too clean is might help cause allergies and asthma. So is there any equilibrium between keeping ourselves obsessively clean and learning to live with the bacteria all around us? All microbes are not bad. The idea is that for many children in the wealthy world, a lack of exposure to bacteria, viruses, and allergens prevents the normal development of the immune system, ultimately increasing the chance of disorders in them. This is called the hygiene hypothesis. "A child's immune system needs education, just like any other growing organ in the human body," The hygiene hypothesis emerged as a tentative explanation to a massive shift in the human disease spectrum from infections to allergies (Ege and Rompa, 2016). The hypothesis borrowed its name from a hypothesis originally proposed to explain the appendicitis epidemic of the early 20th century by an immune system not adequately trained for infections in the 1980s (Barker, 1985). In 1989 David Strachan suggested that allergies might be prevented by viral infections transmitted by "unhygienic contact" to siblings early in life (Strachan, 1989), against the then prevailing idea that viruses triggered allergies (Busse, 1989). This idea was supported by subsequent studies disclosing the inverse associations between allergies and endemic infections by bacterial, viral or protozoic pathogens, such as *Helicobacter pylori*, *hepatitis A virus*, or *Toxoplasma gondii*, which are mostly transmitted by the fecal-oral route (Matricardi, 2000). In the late 1990s, the hygiene hypothesis gained momentum with

the striking farm effect on asthma and allergies and its obvious relation to microbial exposure (Braun-Fahrlander *et al.*, 2002). Finally, a theoretical foundation for the hygiene hypothesis was provided by the emerging T-helper cell type (Th) 1/Th2 paradigm (Holt, 1994), and thereafter with several amendments, the co-occurrence of Th1- and Th2-dominated diseases in the same individual and the simultaneous rise in prevalence of both conditions could be integrated in a larger concept of pro- and anti-inflammatory processes (Bach, 2002; Jutel and Akdis, 2011). Similarly, the hygiene hypothesis itself underwent several modifications. The "disappearing microbes" (Blaser and Falkow, 2009) and the "old friends" (Rook, 2009) hypotheses are principal revisions of the hygiene hypothesis. With a somewhat different slant, they both highlight the role of evolutionary adaptation to microorganisms, regardless of whether they are commensals, symbionts, or pathogens. According to these hypotheses, we are missing their friendship, because extreme cleanliness means that often we don't come in contact with microbes in the same way that our ancestors did and that our immune systems as a whole evolved in the presence of bacteria, viruses, and small animals that naturally inhabit our bodies. In addition, both approaches also endeavor to extend the hygiene hypothesis to autoimmunity, inflammatory disorders, and even to some forms of cancer.

Dirty hands as considered as one of the most likely reasons of passing infections between us by the scientists. The rubbing with soap detaches the germs from your skin, while the rinsing takes them off the hands. But not all of our body has to be washed so rigorously. Overall obsessive rigorous washing disrupts the normal flora which keeps us healthy by competing with harmful organisms. Hence, obsessive washing of hands and excessive

hygienic measures because may result in developing immunologically virgin population which is not exposed to the environment. This may lead to lesser development of immune system and thus make the population more susceptible to the infections and allergies, which may be a major reason behind occurrence of epidemic or maybe pandemic. Although many doctors opposes this theory but many support this theory too. Therefore, obsessive washing of hands and excessive hygienic measures should be avoided and optimum hygienic measures should be followed.

### **Case study-COVID19**

It has been observed that immunocompromised patients, such as recipients of solid-organ transplantation are at a high risk for SARS-CoV-2 infection and poor associated outcomes (Pereira *et al.*, 2020). During the outbreak of COVID-19 in the US, a greater proportion of deaths occurred among African Americans (van Dorn *et al.*, 2020). This is supposed to be because of their sub-standard living which prevents African Americans to follow social distancing because of crowded housing. Most of them have high prevalence of underlying disease conditions like diabetes, asthma, cardiovascular diseases etc. So they are more prone to the infection. However, to know the exact cause behind this, further studies are required (Adams *et al.*, 2020). The pandemic, COVID-19 appears to be more severe in patients with underlying disease conditions like hypertension, cardiovascular disease, and diabetes (Guan *et al.*, 2020).

During pandemic influenza A (H1N1) in 2009, several studies have addressed the serious consequences of Influenza infections in immunocompromised patients, such as recipients of solid-organ transplantation (Kumar *et al.*, 2010; Cordero *et al.*, 2012).

It has been observed during Middle East Respiratory Syndrome (MERS) outbreak that high mortality rates in family-based and hospital-based outbreaks were reported among patients with comorbidities such as diabetes and renal failure (Singh, 2016). SARS also follow the similar trend (de Wit *et al.*, 2016).

In a study, the characterization of a draft genome of *Yersinia pestis* from victims of the Black Death demonstrated that the role of host susceptibility has to be considered in the epidemiology of historical infections (Bos *et al.*, 2011). The influences of frailty, age, gender, and socioeconomic status on plague-related mortality were recently reevaluated by paleodemographic methods (DeWitte and Wood, 2008; DeWitte, 2009; DeWitte, 2010; Castex and Kacki, 2016) and by the direct and extensive analysis of historical sources (Cohn and Alfani, 2007) combined with the calculation of fatality rates (Borsch and Sabraa, 2017) or of individual's risk of death (Alfani and Bonetti, 2019). Similarly Cholera outbreak was found to occur more in socio-economically poor people (Bwire *et al.*, 2017). The risk for cholera in a district was found to be negatively associated with the coverage of literate persons, households using treated water source and owning mobile telephone, and positively associated with the coverage of poor sanitation and drainage conditions and urbanization level in the district (Ali *et al.*, 2017).

So from the above studies it is clear that in pandemic, immuno compromised people have higher susceptibility as well as severity of disease is also very high in them. Comorbidities like Diabetes mellitus has been classified as a cause of secondary immunodeficiency by the World Health Organisation. It has been considered a risk factor for recurrent infection (Johnston *et al.*, 2000).

Immunosuppression may increase the frequency of hyperlipidemia, diabetes, and hypertension as well as it has positive impact on the development of metabolic comorbidities (Watt, 2011). It is also clear that socio-economically poor people are more susceptible, this can also be explained on the basis of immunodeficiency. As discussed earlier, people in developing countries especially people living on outskirts are at higher risk of exposure to various chemicals i.e., environmental pollutants that weakens their immune system. As well as due to their sub-standard living they don't have access to adequate housing and hygiene. Malnutrition is also a cause of weakened immune system as both humoral and cell mediated immune responses are reduced in malnutrition (Benenson, 1981; Baveja, 2005). So in an immuno compromised population, the disease susceptibility is high which causes rapid progression and wide range transmission of the disease which may be a major cause behind occurrence of pandemic.

SARS-CoV-2 is a zoonotic  $\beta$ -coronavirus, which enters cells via binding of S (spike) protein of its envelope to the human angiotensin-converting enzyme 2(hACE2) after S protein cleavage by host serine protease TMPRSS2 [Ou *et al.*, 2020; Rivellese and Prediletto, 2020]. hACE2 is expressed on type II alveolar cells (constituting about 80% of all hACE2-expressing cells), nasal mucosa, upper respiratory tract, kidney, endothelium, heart, and intestine cells (Donoghue *et al.*, 2000; Zou *et al.*, 2020]. Another receptor, CD147, has shown to be involved in mediating host cell invasion by SARS-CoV-2 (Wang *et al.*, 2020). SARS-CoV-2 impairs innate and adaptive antiviral responses, triggers hyperinflammation, and deranges the renin-angiotensin-aldosterone system (RAAS), all culminating to promote detrimental hypercoagulability and immunothrombosis

(Henry *et al.*, 2020). Cytokines play central role in the pathophysiology of COVID-19, some of them are beneficial (type-I interferon, interleukin-7), while others appear detrimental (interleukin-1 $\beta$ , -6, and TNF- $\alpha$ ). Concomitant immunodeficiency has emerged as another characteristic of the disease, particularly involving impaired type-I interferon response, and lymphopenia. Recent data have suggested that SARS-CoV-2 through receptor-dependent, S protein-mediated membrane fusion can directly infect T cells (Wang *et al.*, 2020). However, T cells have a very low expression level of hACE2, suggesting either high S protein affinity for hACE2 or an alternative receptor. T cell infection caused by SARS-CoV-2 is abortive, which means SARS-CoV-2 virus does not replicate within T cells but rather induces cell death (Wang *et al.*, 2020). In SARS-CoV infection, the modulation of TNF- $\alpha$ -converting enzyme (TACE or ADAM17) occurs by the spike protein of SARS-CoV and hACE2, which induces TNF- $\alpha$  production which may accentuate T cell apoptosis (Haga *et al.*, 2008; Mehta *et al.*, 2018). Upregulation of autophagy, apoptosis, and p53 pathways in peripheral blood mononuclear cells (PBMCs) were recorded from COVID-19 patients, when compared to healthy controls (Xiong *et al.*, 2020). In epidemiological studies, an elevation of acute phase reactants in patients with COVID-19, including C-reactive protein (CRP), s ESR, serum amyloid A, and ferritin have been demonstrated indicating a rapid activation of the innate immune response [3,23–25]. Accordingly, COVID-19 patients have high levels of circulating TNF- $\alpha$ , IL-1 $\beta$ , IL-1Ra, sIL-2Ra, IL-6, IL-10, IL-17, IL-18, IFN- $\gamma$ , MCP-3, M-CSF, MIP-1a, G-CSF, IP-10 and MCP-1 (Huang *et al.*, 2020; Yang *et al.*, 2020). These results are suggestive of hypercytokinemia, which is a hallmark of COVID-19. Nonetheless, to discriminate between mild, moderate, and severe cases only the serum concentrations of certain of

these cytokines are indicators (mainly IL-1  $\beta$ , IL-1Ra, IL-6, IL-7, IL-10, IP-10, and TNF- $\alpha$ ) (Yang *et al.*, 2020). Thus, hypercytokinemia should be regarded as a general marker of SARS-CoV-2, while the term 'cytokine storm' is used for those situations of overly exuberant inflammation leading to critical conditions, such as ARDS, disseminated intravascular coagulation or multiple organ failure. Also in COVID-19 patients high levels of chemokines and their coupled receptors have been observed (Xiong *et al.*, 2020; Huang *et al.*, 2020; Yang *et al.*, 2020). Accordingly, analysis of the molecular signature within the bronchioalveolar lavage fluids (BALFs) of patients revealed an overabundance of upregulated chemokine transcripts, including neutrophil recruiting mediators (CXCL1, CXCL2, CXCL8, CXCL10, CCL2, CCL7) and other attractants of monocytes and immune cells (CXCL6, CXCL11, CCL2, CCL3, CCL4, CCL7, CCL8, CCL20) (Zhou *et al.*, 2020). These results are consistent with pathological findings attesting to lung infiltration by monocytes, macrophages and neutrophils, in contrast with lower amounts of lymphocytes (Yao *et al.*, 2020). Immunosenescence may account for a reduced type-I IFN response and thus greater severity of COVID-19. Accordingly increased age is associated with a poorer outcome [Fu *et al.*, 2020; Huang *et al.*, 2020; Zhou *et al.*, 2020]. Mild/moderate infection by SARS-CoV-2 is characterized by the robust expression of ISGs in patients' BALFs and is associated with a potent type-I IFN response (Zhou *et al.*, 2020). Moreover, preliminary results from patients with mild/moderate to severe forms during the first week of COVID-19 have revealed early IFN production in peripheral blood (Trouillet-Assant *et al.*, 2020). In contrast, no IFN production was displayed in about 20%. In another study it was found that in mild-to-moderate patients, type-I IFN response was high (between days 8-12) while reduced in more severe patients

who had a striking down regulation of IFN-stimulated genes (Hadjadj *et al.*, 2020). Lymphopenia has been observed in over 80% of patients and it is one of the most prominent markers of COVID-19 [Chen *et al.*, 2020; Huang *et al.*, 2020; Wang *et al.*, 2020]. Investigations have shown that all subsets of lymphocytes were decreased, including CD4+ and CD8+ cytotoxic T cells (Diao *et al.*, 2020; Hadjadj *et al.*, 2020) memory and regulatory T cells, natural killer (NK) cells (Qin *et al.*, 2020), along with B cells (Wang *et al.*, 2020). Lower lymphocyte counts are closely linked to severe disease (Qin *et al.*, 2020; Wang *et al.*, 2020). T cells show elevated exhaustion levels and reduced functional diversity in addition to being quantitatively decreased (Diao *et al.*, 2020; Zheng *et al.*, 2020). Quantitatively T-cells are negatively correlated with serum IL-6, IL-10 and TNF- $\alpha$  and with higher levels of exhaustion markers, such as PD-1 or Tim-3 (Diao *et al.*, 2020; Hadjadj *et al.*, 2020; Wherry and Kurachi, 2015). Patients with severe form of COVID-19 have more non-functional CD4+ T cells and less multifunctional, as well as they have fewer nonexhausted CD8+ T cells than patients with mild COVID-19 (Zheng *et al.*, 2020). In late stages of COVID-19 (around 7-10 days), sudden and rapidly progressing clinical deterioration has been widely mentioned. This often manifests as an unexpected exacerbation of symptoms and is correlated with increased levels of acute phase reactants (ESR, CRP, ferritin), coagulopathy (elevated titers of d-dimers, disseminated intravascular coagulation), and cell lysis (CK, LDH) (Huang *et al.*, 2020; Wang *et al.*, 2020; Zhou *et al.*, 2020). Clinical and laboratory parameters in the most severe patients are correlated with increased levels of proinflammatory cytokines (IL-1 $\beta$ , IL-1Ra, IL-6, TNF- $\alpha$ , and sIL2-R $\alpha$ ), evocative of a cytokine storm (Zhou *et al.*, 2020; Mehta *et al.*, 2020; McGonagle *et al.*, 2020; Chen *et*

*al.*, 2019). It was observed that ARDS occurs in SARS-CoV patients even with a diminishing viral load, suggesting that rather than viral virulence, exuberant host immune response may be responsible for this outcome. Such a cytokine profile is strongly reminiscent of both hemophagocytic lymphohistiocytosis (HLH) and Cytokine Release Syndrome (CRS) (Borrega *et al.*, 2019; Ramos-Casals *et al.*, 2014).

Similar to what is observed in SARS-CoV-2 infection, the immunodeficiency related to abnormal T cell number or function appears to be the prime source of most cytokine storms (Bracaglia *et al.*, 2017; Crayne *et al.*, 2019; Filipovich, 2011; Stepp *et al.*, 2011). However, for the state of primary hyperactivated innate immunity an alternative pathway is possible, presumably this cytokine storm occurs due to the combination of a defective (or delayed) first line of defense, followed by dysfunctional T cell response (generally cytotoxicity) and persistent hypercytokinemia (IL-6, IL-1 $\beta$ , and TNF- $\alpha$ ). This results in an impaired clearance of infected/activated macrophages or apoptic cells, an increase in viral replication and dissemination, followed by an IL-18/IFN- $\gamma$  feed forward loop activating macrophages, culminating in multiple cytokine release, hemophagocytosis, coagulopathy, and ARDS (Schulert and Grom, 2015; Brisse *et al.*, 2016; Crayne *et al.*, 2019).

Some of these mediators including macrophage activation by the H-chain of ferritin or NK cell function impairment by IL-6 (Giamarellos-Bourboulis *et al.*, 2020) may further fuel this vicious cycle (Rosário *et al.*, 2013; Ruscitti *et al.*, 2015; Shoefeld, 2020). After more precise analysis of the immunopathology of SARS-CoV2-related ARDS, it was concluded that in worsening COVID-19, two patterns of immune dysfunction exist: (i) one pattern with IL-6

driven immune dysregulation and (ii) one pattern highly suggestive of IL-1 $\beta$  driven macrophage activation syndrome (hyperferritinemia and elevated H score : 25% of patients) (Giamarellos-Bourboulis *et al.*, 2020). Immune dysregulation is found to be characterized by a combination of hypercytokinemia, global lymphopenia (including CD4+ and NK cells) and immunoparalysis (as indicated by decreased HLA-DR molecules on CD14 monocytes). Since, at present the most urgently awaited and needed determinants are the factors to predict progression of disease toward severe forms hence, a highly-structured approach, comprising of immune monitoring, would thus be of utmost importance.

#### **Convalescent plasma treatment: an alternative treatment for COVID-19 patients**

Convalescence is the period of recovery following acute illness or injury that begins early after the acute phase of illness and continues until complete cure or rehabilitation has been attained (Zazeela, 1951). 81.2% (311 of 383 patients) of convalescent clinically diagnosed SARS-CoV(1) patients were tested positive for serum SARS-CoV(1) IgG. In this study misdiagnosed disease among the seronegative patients was not excluded. (Xie *et al.*, 2005).

In another study, SARS-CoV(1) IgG and neutralizing Ab have been found to peak at 4 months and then afterwards began diminishing and reached undetectable levels in 25.6% (IgG) and 16.1% (neutralizing Ab) of 56 patients at 36 months of follow-up (Cao *et al.*, 2007). Furthermore, it is been found that there is a correlation between the titers in convalescent patients and the initial viral load and titers are independently associated with severity of the viral illness both in H1N1 and MERS-CoV patients (Ko *et al.*, 2007; Hung *et*

*al.*, 2010). Besides, to improve the survival rate of patients with severe acute respiratory syndromes of viral etiology, convalescent plasma treatment, i.e. passive polyclonal antibody (Ab) administration to provide immediate immunity, has been used (Mair-Jenkins *et al.*, 2015). Indeed, a number of studies, have reported positive outcomes of convalescent plasma treatment, including decreased mortality in the Spanish Influenza A (H1N1) infections in 1915-1917 (Luke *et al.*, 2006), recent Influenza A (H1N1) infections in 2009/2010 (Hung *et al.*, 2011), and more importantly, SARS-CoV infections in 2003 (Cheng *et al.*, 2005).

The numbers of CD4+ T cells, CD8+ T cells, NK cells and B cells and the markers of exhaustion on cytotoxic lymphocytes normalize in patients who have recovered from COVID-19 or are convalescent (Chen *et al.*, 2020; Zheng *et al.*, 2020). Additionally, SARS-CoV-2-specific antibodies can be detected in them. The identification of SARS-CoV-2-specific neutralizing antibodies has been allowed through high-throughput platforms, such as the large-scale single-cell RNA sequencing of B cells (enriched for B cells that produce antibodies directed at the SARS-CoV-2 spike glycoprotein) from patients who are convalescent.

To treat a small number of critically ill patients with COVID-19 who developed ARDS, convalescent plasma containing neutralizing antibodies has been used and clinical improvement was seen in all the five critically ill patients (Shen *et al.*, 2020). Yet so far, no specific treatment has been proven to be effective for COVID-19. Treatment is currently mainly supportive, with in particular mechanical ventilation for the critically ill patients (6.1% in a series of 1099 cases in China) (Guan *et al.*, 2020). Novel therapeutic approaches are an exigency. In this context, the therapeutic potential associated with

convalescent plasma needs to be explored (Chen *et al.*, 2020; Casadevall and Pirofski, 2020).

### **Can chemical drugs be helpful in containment of pandemics?**

The pandemic caused by bacteria like plague, is treatable with commonly available antibiotics. The earlier a patient seeks medical care and receives treatment that is appropriate for plague, the better their chances are of a full recovery (US CDC, 2019). Even then 100% containment is not possible by giving treatment only because re-infection is common in pandemics due to its rapid progression. However, for the pandemics caused by viruses, antibiotics are ineffective like for COVID-19, there are no medicines that have been shown to prevent or cure the disease. Several drugs including lopinavir-ritonavir, remdesivir, hydroxychloroquine, and azithromycin have been tested in clinical trials (Cao *et al.*, 2020; Gautret *et al.*, 2020; Zhou *et al.*, 2020) but none of them have been proven to be a definite therapy.

Hence, for viral pandemic diseases treatment is essentially supportive and symptomatic. Hence, without availability of specific drugs for treatment, containment is not possible. For containment of any pandemic an amalgamation of rapid diagnosis, prevention and control, case management i.e. treatment and mass vaccination is required (WHO,2010). Because of their changing antigenic type vaccine development is strenuous job. As the vaccine develops against one antigenic type, the pathogen undergoes antigenic change and therefore does not respond to that vaccine. While, para-specific vaccines showing Non-specific effects (also called "off-target effects" or "heterologous effects") may be a potential tool to manage pandemics. The effects which go beyond the specific protective effects

against the targeted diseases are called off-target effects. By increasing protection against non-targeted infections, non-specific effects can be strongly beneficial, but can also increase susceptibility to non-targeted infections (Benn *et al.*, 2013; Shann, 2013). A study showed, in the absence of a specific vaccination against Covid-19, population-based BCG vaccination may have a role in reducing the impact of this disease and is being studied in a prospective trial (Hegarty *et al.*, 2020). Prevention, control plays a major role in containment of pandemics mainly owing to isolation and quarantine (WHO,2020). Travelling population is found to be a major reason behind the occurrence of pandemic.

As of date 8th June 2020, the date of preparation of this paper, a total of 2,60,093 people have been affected in India; of which 1,25,641 (48.30%) have recovered, 1,27,189 are active and 7,263 (2.79%) have deceased, according to the news update. Therefore, the mortality rate for COVID-19 is 2.79 % compared to 11% for SARS-CoV and 34.4% for MERS-CoV. The total number of cases of COVID-19 in the world were 71,24,043 with 34,78,161 (48.82%) recoveries and 4,06,785 (5.71%) mortality (<https://www.worldmeters.info>).

### **Role of ayurveda or naturopathy in control of pandemics**

As Immunodeficiency decreases the resistance and increases susceptibility to infection (Benenson, 1981). Therefore the best way to deal with pandemic is to strengthen our immune system. Ayurveda gives prime importance to prophylaxis. There are many natural herbs and ingredients which are known to strengthen our immunity. Mineral pitch (MP) which is a traditional medicine is proposed to boost immunity in conditions that suppress Th1 cytokines.

It is found to elicit a dose-dependent Th1 immune response (Rubab *et al.*, 2013). Almond oil has many properties including anti-inflammatory, immunity-boosting (Ahmad, 2010). In a study, The extract from bark and root of Salacia of the family Hippocrateaceae (*Salacia reticulata*, *Salacia oblonga*, etc.) which have been used for traditional Ayurvedic medicine have shown to exert bioregulatory functions by boosting intestinal immunity (Oda *et al.*, 2011).Curcumin is the bioactive pigment of turmeric, in some studies have indicated that this phytochemical could target regulatory T cells and convert them into T helper 1 cells and thus enhances immunity (Shafabakhsh *et al.*, 2019).

In a study, ayurvedic perspective on preventive medicine in children is shown with specific reference to vaccination. The study explored alternative approaches to boost immunity in children. I this land of over 1 billion population, universal immunization program of Government of India have only 30 to 40 %. Availability, efficacy and safety of preventive measures in the form of vaccines come under doubt now and then. We can prevent the diseases by using methods and principles of Ayurveda and contain the sufferings of the large population in India. Prophylactic methods of Ayurveda can change maternal health scenario in the country with children and mothers dying from malnutrition and diseases, (Nanal, 2008).

Ayurveda have several strong points in preventive care like scope of prevention is very large, no or very minimum side or after ill effects are seen, it takes care of mind and related disease, rasayan practices in Ayurveda can be safely promoted as well as individuals can also participate in their own health management, instead of being only passive patients. Now, it is the time to analyze the knowledge resources of our traditional

medical systems, and though a visionary policy reforms and committed political will we should make it available to the people in our society.

### **Nutritional factors and immunomodulation**

To reduce the immunodeficiency, there are some of the nutrients which are necessary for the body system. These may be minerals (trace materials), vitamins, roughages, antioxidants, lipids, Carbohydrates, Proteins, Ionophores, Carotenoids, Bioflavenoids, Omega-3 fatty acids, etc. All these are necessary for the development of the body to improve the nonspecific and specific immunity (Table 1).

An adequate supply of good quality of protein containing essential amino acids, certain vitamins, minerals, and trace elements are must to ensure protection of body and health against infectious diseases through successful operation of the immune mechanism. Demands for these nutrients are greatly increased during the production of immunity following diseases/vaccinations. The nutrient discussed the best guidelines during a generalized immune response. Clearly, then, the way is open to a better understanding of how synergistic application of vitamins, minerals, proteins and other nutrients and plant-derived factors can optimize immune function (Chauhan, 2007).

### **Microbial products and immunomodulation**

Crude preparations of some microorganisms are also used as immunomodulator which enhances the both specific and paraspecific immunity in animals and man. The Freund's complete adjuvant derived from *Mycobacterium phlei* is used in nonspecific manner. *Corynebacterium parvum* now classified as *Propionibacterium acnes* has

been associated with immunostimulatory activity in man and domestic animals. The *Propionibacterium acnes* is effective in increasing immunity against bacterial, viral and protozoan infections. It activates the macrophages, increases antibody synthesis, increases T-cell responsiveness and induces cytolytic responses of T-cells against tumor cells. Lentinan, a neutral polysaccharide derived from fungus *Lentinusedodes* is also found to have immunomodulatory property. It was found to stimulate pinocytosis of murine peritoneal macrophages, to increase the production of interferons, to enhance the production of interleukin-1. It enhances both specific as well as paraspecific immunity in animals (Chauhan, 2007).

### **Synthetic chemical compounds and immunomodulation**

In this group, mainly 3 chemical compounds are extensively studied including levamisole, synthetic polynucleotides and isoprinosine. Levamisole was originally developed as an anthelmintic for man and animals. But apart from its anthelmintic activity, it was also found to exert immunopotentiating effect. From the extensive studies, it has been observed that levamisole is having a marked effect on cellular immunity with little effect on antibody production. Also, it is effective only when the animal's immune system is functioning sub optimally. Isoprinosine is a synthetic immunomodulator which is also having antiviral activity. It enhances lymphocyte proliferative responses, increases lymphokine production and increases NK cell cytotoxicity. Immunosuppression caused due to viruses or cyclophosphamide can be restored by isoprinosine treatment. But this has no effect on B-cell proliferation induced by lipo-polysaccharides. Synthetic polynucleotides is a complex of high molecular weight and was found to augment natural killer cell activity, activate

macrophage tumoricidal activity, stimulate lymphocytes to PHA and enhance delayed type hypersensitivity responses to sheep red blood cells. Polynucleotides have dual effect on antibody production; if antigen is administered within hours of polynucleotide administration, helper cells tend to dominate the response, whereas if antigen administration is delayed to 24 hrs it leads to immunosuppression. The inherent toxicity of polynucleotides tends to limit their usefulness as therapeutic immunomodulators in animals. The toxic effects of polynucleotides include pulmonary thrombosis, hepatic neurosis, reduced body weight, elevated blood urea nitrogen and leucopenia.

### **Herbal immunomodulation**

In Ayurveda, the life describes four types of therapeutic approaches namely PrakritiSthapanam (maintenance of health), Roganashanichikitsa (cure of disease), Naishtikichikitsa (spiritual therapy) and Rasayanachikitsa (herbal product therapy). The rasayana therapy is useful for preventing the diseases. The rasayana drugs are endowed with multiple properties like delaying ageing, improving mental functions and preventing diseases. There are many herbs which are known to exert their immunomodulatory properties, of which some of them are studied scientifically but most of them are yet to be scientifically validated. *Tinosporacordifolia*, *Withaniasomnifera*, *Asparagus racemosus*, *Emblica officinalis*, *Piper longum*, *Terminalia chebula*, *Borrheviadiffusa* and *Acorus calamus* are found to be immunostimulant in different models of immunosuppression or infections. *Tinosporacordifolia* prevented cyclophosphamide induced immunosuppression as well as immune response in suppressed mice. These herbs exhibited an array of diverse biological activities such as antistress, adaptogenic, anti-ageing and immunomodulatory activity.

The extract of *Azadirachtaindica* (neem) is found to stimulate the phagocytic activity and antigen presenting ability of macrophages and enhances the mitogenic response of splenocytes to ConA. Besides, it is also effective against allergic disorders and desensitizes the host to specific allergens limiting the danger of anaphylactic reactions. The *Piper longum* (pipali) is found to be effective in prevention and control of giardiasis in human beings (Chauhan and Tulsa Devi, 2020).

### **Cowpathy in immunomodulation**

Cowpathy is an age old system of medicine described in ancient Indian literature 'Ayurveda' as 'Panchgavya Chikitsa'. In Ayurvedic system, medicines are prepared either from plants or from animals besides the use of certain metals. The Ayurvedic medicines of animal origin are mainly prepared from cow products. The high profile medicine 'Panchgavya' is prepared from five materials received from a cow that includes milk, Dahi (curd), Ghee (butter oil), urine and dung. Cowpathy is just like any other system of medicine such as Homeopathy, Allopathy or Naturopathy. In this, the human or animal ailments are treated with products of cow also known as Panchgavya. In recent years, interest has been generated among scientific community of the world to develop or scientifically validate the Indigenous Technical Knowledge (ITK) as an alternate therapeutic or preventive approach. As is evident from the trends of modern allopathic treatments particularly the development of resistance in microorganisms and side effects, the alternative system of medicine gains momentum not only in India but WHO also established recognition to such systems. In fact in the western world also, scientists/clinicians are facing problem in handling the multiple drug resistance in microorganisms, presence of antibiotic residues in food chain

and/or associated allergies and autoimmune disorders in man (Chauhan, 2017a). As per WHO, the twentieth century wonder drugs “antibiotics” will not remain useful and become almost ineffective by the year 2020, then one has to think over the alternative therapeutic approaches to control the infections. In fact most of the antibiotic drugs are bacteriostatic in nature and as such they do not kill the bacteria rather they stop or check their growth and bacteria have to be destroyed by the body’s own defense mechanism known as “Phagocytic System” through macrophages (monocytes of the blood). During last few years it has been observed that the efficiency of these macrophages reduced drastically as a result of the environmental pollution and presence of pesticides, heavy metals, fungal toxins etc. in the food chain. That is attributed to the heavy use of agrochemicals in agriculture and poor storage conditions of food grains. Anyhow deficient functioning of macrophages leads to inefficacy of antibiotic drugs, development of resistance in bacteria, recurrent infections, and or decreased immune status of an individual.

Recent researches showed that cow urine enhances the immune status of an individual through activating the macrophages and augmenting their engulfment power as well as bactericidal activity. This research opened a new era in medical science and CSIR has got a patent from US on cow urine for its bio-enhancing properties and its use in tuberculous patients (Dhama *et al.*, 2005). Along with traditional therapy of tuberculous drugs, if one also consumes cow urine, the anti-tuberculous drugs act faster even in low doses and thereby reducing the cost of treatment and its duration. It had been recorded that use of cow urine along with the antibiotics prevents the development of resistance in microorganisms against the antibiotics.

This is thought that the cow urine blocks the R-factor, a part of plasmid genome of bacteria responsible for the development of antibacterial resistance. It has been found to enhance the body’s immunity and resistance power to fight with infections. Cow urine has antioxidant properties and thus it neutralizes the oxidative stress produced in body through action on free radicals. It has been found to repair the damaged DNA and thus is effective for the cancer therapy. Scientists proved that the pesticides even at very low doses cause apoptosis (cell suicide) in lymphocytes of blood and tissues through fragmentation of DNA and cow urine helps the lymphocytes to survive and not to commit suicide, it also repairs the damaged DNA. Besides, in poultry cow urine enhances the immunocompetence of birds and provides better protection along with vaccination (Chauhan, 2004).

On the basis of chemical fingerprinting through modern equipment like HPLC, it has also been observed during the scientific research that the urine of Indian cows are highly effective and almost nil or few medicinal properties are present in the urine of crossbred, exotic cows, buffaloes, etc. The Indigenous cow urine contains “Rasayan” tatva, which is responsible to modulate immune system and act as bioenhancer (Chauhan, 2013). The ability of indigenous cow urine is tested for its immunomodulatory properties in mice, rat and avian lymphocyte cell culture system for the first time and the results are presented in Table 2.

### **Biological warfare: A possible cause of upcoming pandemic**

Through the infectivity of disease-causing infectious agents, the intended target effects are achieved by biological weapons. The Biological and Toxin Weapon Convention has prohibited the ability to use biological agents in warfare.

Bioterrorism is defined as the deliberate release of viruses, bacteria or other agents used to cause illness or death in people, but also in animals or plants. Biological agents include microorganisms or biological toxins that are used to produce death in humans, animals and plants. They are characterized by low visibility, high potency, substantial accessibility and relatively easy delivery (Agarwal *et al.*, 2004). Biological warfare is aimed at creating societal disruption, terror, casualties or economic loss, inspired by religious, ideological or political beliefs. The measure of societal disruption and panic, and not necessarily mere the number of casualties is the defining feature of the success of bioterrorist attempts. Thus, making only a few individuals ill by the use of crude methods may be sufficient, as long as it creates the impact that is aimed for (Dhama *et al.*, 2012; Jansen *et al.*, 2014).

### **What we should do in case of biological warfare?**

Successful management of exposure to Biological warfare agent relies on early diagnosis. Medical units should plan on information not only from detectors and intelligence sources, but also from casualties themselves. This applies essentially to biological warfare weapons/agents since at present there are no rapid methods of early identification or detection. Unlike chemical agents, which typically lead to violent disease syndromes at site of exposure within minutes, disease resulting from biological agents have incubation period of days depending upon the agent used (Franz *et al.*, 1997). Most of the attacks are clinically recognized. They are further identified by usual laboratory tests (culture, microscopy, ELISA, animal inoculation methods, mass spectroscopy, PCR, antibodies detection (e.g. IgM) and by detection of metabolic products of infections/toxic agents in clinical specimens.

Triage is done as whether emergency medical treatment or decontamination requires priority. It is classified as immediate, delayed or minimal. Immediate includes casualties who require lifesaving care within a short time, when that care is available and of short duration. Delayed includes Casualties with severe injuries who are in need of major or prolonged surgery or other care and who will require hospitalization, but delay of this care will not adversely affect the outcome of the injury and minimal includes casualties who have minor injuries, can be helped by non-physician medical personnel, will not be evacuated, and will be able to return to duty shortly. Emergency Medical Treatment (EMT) and decontamination may be performed in rapid sequence. Treatment follows the universally accepted breakthrough of first ensuring the adequacy of airway breathing and circulation (Keim and Kaufmann, 1999). The physical process of removing residual chemicals from persons, equipment and the environment is known as decontamination. Every person arriving at Medical Treatment Facility (MTF) from biological warfare contaminated area is considered contaminated unless there is positive proof to contrary (Tucker, 1997; Richards *et al.*, 1999). After the identification and decontamination of casualties, measures must be taken to prevent contamination of ambulance and air evacuation assets. Many BWA casualties may be safely evacuated using basic infection control guidelines (Sidell *et al.*, 1997).

Prevention is done by active immunization, chemoprophylaxis and personal protective equipment. Chemoprophylaxis and vaccinations are discussed in Table 1. The primary responsibility of those who treat victims of BWAs is to protect themselves by wearing adequate protective equipment (Wiener, 1996). However, even if the number of casualties is likely to be limited, due to

societal disruption the impact of a bioterrorist attack can still be high. The ability of society to combat 'regular' infectious diseases outbreaks, as well as mitigating the effects of bioterrorist attacks will be improved by measures aimed at enhancing diagnostic and therapeutic capabilities and capacities alongside training and education (Jansen *et al.*, 2014).

### **Lessons from pandemics till today and preparation for upcoming pandemics**

The pandemics we have experienced so far have shown a number of deficiencies and defects, including vulnerabilities in global, national, and local public health capacities; difficulties in decision making under conditions of uncertainty; limitations of scientific knowledge; complexities in international cooperation; and challenges in communication among experts, policymakers, and the public. The pandemics presented a public health emergency of uncertain scope, duration, and effect. These showed that there is a lot of scope for improvement in public health sector. Our ability to detect and predict the initial emergence of a novel human pathogen (for example, the spillover of a virus from its animal reservoir to a human host), and our capacity to observe and forecast the transmission and spread of that pathogen within and among human populations, remains limited (Shaman, 2018). Despite their considerable effects on global public health and growing understanding of the process by which they emerge, no pandemic has been predicted before infecting human beings (Morse *et al.*, 2012). Almost all of the previous studies have examined that during pandemics, huge economic losses in terms of income and the loss associated with mortality risk is faced by every country. The World Bank, for example, generated estimates of global income losses under different influenza pandemic scenarios (Morse *et al.*, 2012;

Jonas, 2013). For the past two decades, strengthening of public health surveillance worldwide to provide early warning has been the primary recommendation of expert groups for emerging infections (Oaks *et al.*, 1992; Morse *et al.*, 1996; National Research Council, 2010). Targeted global surveillance of emerging and previously unknown infections in both human beings and other species is enabled by technological advances in mathematical modelling, communication, diagnostics and informatics enable. New risk-assessment approaches show promise for the use of these capabilities to predict and pre-empt potential pandemics at their source (example- in wildlife or other animals), and need to be further developed. It has been proved now beyond any doubt that the allopathic system of medicine alone may not be able to control any such pandemic or epidemic. Now we should devise a mechanism of a holistic approach consisting of our ancient Ayurveda, Naturopathy, Yoga, Cowpathy and modern allopath; and it will be further better if the ancient knowledge proven on modern parameters is used without hesitation which may reduce morbidity and mortality. This will not only reduce the anxiety and tension in the community but also provide the confidence in the front line health workers and boost their morale in the society.

### **Iceberg of disease: phenomena which should not be overlooked**

According to the iceberg phenomena of disease, disease in a community may be compared with an iceberg. The floating tip of the iceberg represents what the clinical cases i.e., what physician sees in the community. The vast submerged portion of the iceberg represents the hidden mass of disease, i.e., what remains unseen which includes pre-symptomatic, inapparent, latent and undiagnosed cases and carriers in the community.

**Table.1** Nutrients and Immunomodulation

	<b>Nutrients</b>	<b>Immunomodulation</b>
1.	Boron (Fruits and vegetables, cabbage and grains)	<b>Enhance Brain Function, Immunopotiation</b>
2.	Calcium (Soybean, peanut, sardine, sunflower seeds, dried beans, grains and unrefined cereals)	<b>Helps to maintain proper nerve and muscular function, protecting immune system</b>
3.	Chromium (Molasses, whole grains)	<b>Increase <i>in vitro</i> lymphocyte proliferative responses to ConA</b>
4.	Cobalt (Vitamin B-12 supplements)	<b>It helps to form the red blood cells, maintain nerve tissues, protecting immune system.</b>
5.	Copper (Molasses, nuts, seeds)	<b>Protection of the tissues against free radicals.</b>
6.	Iodine (Sea foods, seaweeds like kelp)	<b>Influences the nutrient metabolism, nerve and muscle functions, protecting immune system.</b>
7.	Germanium (Garlic, mushrooms, onion, aloe vera, comfrey, ginseng)	<b>Saves the body from harmful toxins and poisons, reducing damage from radioactivity, protecting immune system.</b>
8.	Magnesium	<b>Key substance for proper functioning of the nervous system. Enhance natural killer cell and macrophage activity.</b>
9.	Molybdenum	<b>Key for growth and development of the nervous system, prevent against mental disturbance.</b>
10.	Phosphorous	<b>Key component of DNA and RNA, contribute to tissue growth and repair, nerve impulse, central nervous system health.</b>
11.	Potassium (Whole grains, nuts, dairy products)	<b>Required for protein synthesis and flow oxygen to the brain.</b>
12.	Selenium (Whole grains, asparagus, garlic, eggs, mushrooms, sea food)	<b>Protecting cells and tissues from free radicals. Increases natural killer cells and cancer fighting cells.</b>
13.	Sodium (Salt)	<b>Together with potassium and chloride sodium maintains fluid distribution and pH balance, control; muscle contraction and nerve function.</b>
14.	Sulfur (Peas and beans)	<b>Helps the body to resist bacteria, and protects the protoplasm of the cells, slows down the disintegration of the tissues and cells and slows the aging process.</b>
15.	Zinc	<b>Integral part in the synthesis of DNA and RNA, the genetic material that control cells growth, division and function, immune function.</b>
16.	Copper	<b>Increase the activity of phagocytic cells.</b>
17.	Iron (Green vegetables)	<b>Immune system keeps invading microbes in check by depriving them of iron via a specific immune defense substance called lactoferrin.</b>
18.	Vitamin A (Carrot)	<b>Enhances white blood cell function, enhances resistance to infection and carcinogens.</b>
19.	Vitamin E (cabbage, cauliflower and in green leaves)	<b>It helps to protect vitamin A and red blood cells.</b>
20.	Vitamin B (Externally in the form of B-Complex)	<b>Helps to maintain the healthy skin and well functioning of the nervous system. Immune cell growth and division.</b>
21.	Vitamin C (Fruits and vegetables)	<b>Increases the production of infection fighting white blood cells and antibodies, interferon. Preventing the entry of virus.</b>

22.	Immunoglobulins (IgG) Produced by the B- lymphocytes	<b>It has the capacity to quickly bind with foreign substances leading to opsonization.</b>
23.	Immunoglobulins (IgM) Produced in body during primary immune response.	<b>Neutralize antigen agglutination.</b>
24.	Immunoglobulins (IgA) IgA produced in body surfaces is either secreted on surface through epithelial cells or diffuse in blood stream.	<b>Neutralize the antigen and agglutinate the particulate antigen. Prevents adherence of foreign particles/ antigen on the body surfaces and it can also act inside the cells.</b>
25.	Immunoglobulins (IgE) Very low concentration in serum.	<b>It mediates hypersensitivity type I reaction and is responsible to provide resistance against invading parasitic worms.</b>
26.	Carotenoids (Daily fibrous food)	<b>Increases the number of fighting cells, natural killer cells, and helper T- cells, mops up excess free radicals that accelerating aging, protects against cancer, by stimulating the macrophages to produce tumor necrosis factor.</b>
27.	Bioflavonoid (A wide variety of fruit and vegetables)	<b>Aids the immune system by protecting the cells of the body against environmental pollutants, toxins or germ.</b>
28.	Omega-3-fatty acids (Cod liver oil)	<b>Increasing the activity of phagocytes, the white blood cells, protect the body against damage from over reactions to infection,</b>
29	<b>Arginine</b>	<b>The amino acid l-arginine augments T-cell response and may be helpful in hastening surgical recovery.</b>

**Table.2** Percent increase in immunity through various parameters in comparison to control (Chauhan *et al.*, 2001)

	<b>Parameters</b>	<b>Percent increase in immunity</b>
1.	B-cell blastogenesis	<b>59.5 %</b>
2.	T-cell blastogenesis	<b>64.0 %</b>
3.	Serum IgG level	<b>19.8 %</b>
4.	Serum IgM level	<b>19.0 %</b>
5.	Serum IgA level	<b>0.53 %</b>
6.	Macrophage Functions	<b>104.0 %</b>
7.	DTH reaction	<b>126.0 %</b>
8.	Interleukin 1 level	<b>30.9 %</b>
9.	<b>Interleukin 2 level</b>	<b>11.0 %</b>

The demarcation between apparent and inapparent disease is represented by the "waterline". In some diseases, for example-anemia, malnutrition, mental illness, the submerged portion of the iceberg i.e., the unknown morbidity far exceeds the known morbidity. Thus, an important, undiagnosed reservoir of infection or disease in the community is constituted by the hidden part of the iceberg, and its detection and control is a major challenge which modern techniques

in preventive medicine are facing. One of the major deterrents in the study of chronic diseases of unknown etiology is the absence of methods to detect the subclinical state - the bottom of the iceberg (Lilienfeld *et al.*, 1994). Therefore, to describe health in terms of mortality rates only is misleading. This is because, the burden of ill-health in a community is not revealed by mortality indicators, as for example anemia, mental illness and rheumatoid arthritis.

Therefore, to supplement mortality data, morbidity indicators are used to describe the health status of a population. However, morbidity statistics also have their own shortcomings; they tend to overlook a large number of conditions which are inapparent or subclinical, that is, the hidden part of the iceberg of disease (Park, 2011). Therefore it is clear that we cannot predict how massive the hidden mass of disease can be and how much devastating it can be hence we should focus on immunity enhancement along with looking for agent identification and treatment.

Rapid economic globalization has improved the commercial and technological capabilities and health structure in several countries. However, it has also contributed to the globalization of emerging infectious diseases. Pandemic is a major threat to mankind as well as a topic of global health concern. It encompasses several countries at once. During pandemic, as we do not know how the agent will play out, how to develop a vaccine against the pathogen when it is changing its antigenic form, if developed whether the virus will respond to the vaccine or not and how mass immunization to a population of billions will take place.

So we should strengthen ourselves in terms of our physiological capabilities, immunity. It has been proved now beyond any doubt that the allopathic system of medicine alone may not be able to control any such pandemic or epidemic. Therefore we should opt for an alternate therapy for disease prevention and control via strengthening the immune system. Immunodeficiency being an essential cause in decreasing resistance and increasing susceptibility to infection within the population should be checked. As in today's scenario our lifestyle is exposing us to various chemicals that suppresses our immunity and thereby make us more prone to infections. Now we should devise a mechanism of a

holistic approach consisting of our ancient Ayurveda, Naturopathy, Yoga, Cowpathy and modern allopathy; and it will be further better if the ancient knowledge proven on modern parameters is used without hesitation which may reduce morbidity and mortality. This will not only reduce the anxiety and tension in the community but also provide the confidence in the front line health workers and boost their morale in the society. There is also a need to explore novel therapeutic approach like convalescent plasma treatment which has been shown to be effective in treatment of COVID-19, swine influenza, SARS etc. The pandemics we have experienced so far have shown a number of deficiencies and defects, including vulnerabilities in global, national, and local public health capacities; difficulties in decision making under conditions of uncertainty; limitations of scientific knowledge; complexities in international cooperation; and challenges in communication among experts, policymakers, and the public.

For containment of pandemic, an amalgamation of rapid diagnosis, prevention, control, case management and mass vaccination is required. For forecasting and prevention of upcoming pandemic, global surveillance of emerging and previously unknown infections in both human beings and other species should be done.

It is clear from the Iceberg phenomena of disease occurrence that we cannot predict how massive the hidden mass of disease can be and how much devastating it can be hence we should focus on immunity enhancement along with looking for agent identification and treatment. Preparation beyond planning, with advance protocols and agreements, the commitment of ready reserves of public health experts and a financial line of credit, and the fulfillment of the international health regulations requirements can all help.

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