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Smallest Organism; Highest Threat

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REVIEW

ABSTRACT

Ever since the discovery of virus in beginning of 20th century, infections caused by these organisms have captured attention of researchers. The evolution of viruses is still a controversy, even same for their categorization in either living or non-living. It is clear that besides many controversies virus remains challenging to treat as well as to control in some extent. Though vaccines are available as prophylactic tool and antiviral drugs for treatment, still virus exist in host cells if they successfully invade biological machinery. Now it remains as challenge to treat these smallest organisms with high degree of efficacy and safety. To answer the demand of the present world there is urgent need of more potent and novel drugs for treatment and vaccines to prevent infection. Answer to this problem will definitely reduce casualties occurring worldwide. This review presents few of the pandemics, their causative agents, current status of treatment and future prospective.

Key words: HIV-AIDS, Hepatitis, Influenza, Measles, Rubella.

1. INTRODUCTION OF VIRUSES

Virus is a Latin word meaning "poisonous fluid".[1] There are an estimated 10^{31} viruses in the biosphere and human cells are outnumbered by viruses 100-folds.[2] It is almost more than a century turned since the discovery of viruses brought in noticed.[3] The recorded history of viruses begins in the closing years of the 19th century, but viruses are considered as old as life on Earth. [4, 5]

Viruses are responsible for acute infections, affecting almost all the organs of the body and commonly encountered in medical practice. Until 1939, science was only able to discover and classify 36 antigenically distinct human viruses and even 14 of these could not be propagated regularly in the laboratory.[6] The period of 1940 to 1949 ended up with the development in science by discovery of additional 26 antigenically distinct human pathogenic viruses. Over 90 distinct viruses were discovered, and propagated successfully during 1950 to 1959 with significant advancement of sophisticated instruments and development of newer techniques. Currently laboratory diagnosis of viral diseases have greatly improved with high sensitivity and made more accessible for every class of society since the study of viruses no longer remains a purely academic practice.

Viruses are used to be known as 'filterable agents' to emphasize their small size, all but the largest being visible only in the electron microscope.[7] A complete virus particle, known as a virion, consists simply of nucleic acid protected in a protein coat called a capsid formed from identical protein subunits called capsomeres.[8] Several families of viruses have a structurally different two distinct portions as head and tail. Head portion consist of nucleic acid protected in protein coat and special tube-like structure made up of protein coat called a 'tail', attached to one of the vertices of the shell. The tail is used during fusion of virus with host cell (infection) for penetration through the cell envelope and subsequent DNA translocation from the shell into the host cell where it undergo various stages of replication, multiplication at specific sites. The host cell receptor recognition molecules are attached to the tail, which helps to coordinate the processes of host recognition and DNA delivery (Figure 1).[9]

Thus viruses appear in a behavior of living and non-living nature.[10] They appear as living organism when present in host cell and as non-living when present out of host cells (Figure 2). It is arguable whether they should be grouped as living organisms, since they depend entirely on a host cell for their replication (consider a 'computer viruses' which needs the computer's hardware to act upon) but of the debate of, is virus living or not, viruses are the most Superabundant biological creature on Earth and are able to infect organisms in all three domains of life[11-12] (Archaea Domain, Bacteria Domain, Eukarya Domain); almost every species of animal on earth, from mammals down to insects, protozoa, and even bacteria, as well as plants. Viruses have infected plants and animals, including humans, for millions of years and can be said as most successful parasites.[13]

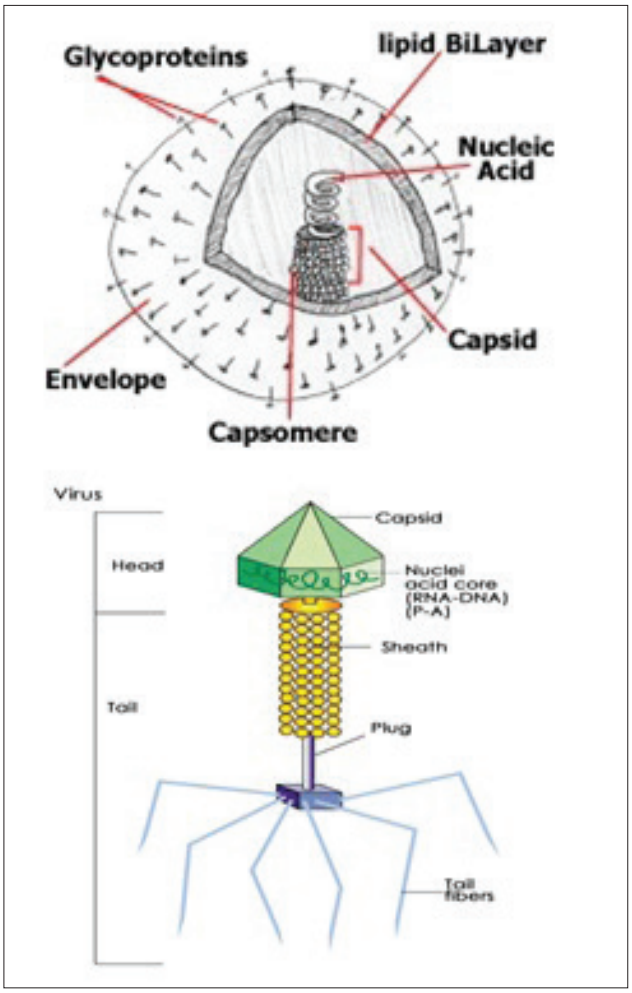

Figure 1. General assembly of Viral Structure

2. EVOLUTIONARY HYPOTHESIS

Contrary to other microscopic to multi-cellular organisms, the origin and evolution of viruses is still to be clear but they may be assumed to occur at a date earlier than the emergence of cells, hardly supported by any means with precise scientific evidences.[14] For example, viruses are not detected as fossil particles, possibly because they are too small and too frail to succumb in fossilization processes and may be because of this evolutionists are struggling to specifically reconstruct an evolutional history of viruses even conserved nucleic acid sequences of viruses have never been detected in fossilized biological materials such as plant leaves or insects.[14-15] However, besides of all the unanswered debate regarding understanding their origin and evolution, several theories were successfully proposed the basic observed facts about viruses. According to a form of natural selection very similar to that governing other living organisms, viruses probably evolved may be due to the fact that the genome of viruses underlies mutation and genetic recombination. In fact this basic fact is strong enough to provide support for scientific satisfaction of some commonly discussed hypotheses on virus origin and evolution. Presently, there are three hypotheses often discussed for virus evolution. The first hypothesis known as the degeneracy hypothesis[17] or reduction hypothesis [12,16] (regressive evolution[18]) assumes that viruses descend from free-living and more complex parasites. According to this theory as like mitochondria that have their own genetic information and replicate on their own, ancestral viruses developed a growing dependence on host-cell intracellular "machinery" through evolutionary time, while retaining the ability to auto-replicate. The second hypothesis known as the vagrancy hypothesis[19] or escape hypothesis[20] (cell origin) which assumes that viruses reproduce their origin from cell DNA and/or messenger RNA, which adopt the capability to auto-replicate, exist and function independently. Finally, there is the theory of virus-first hypothesis[16] (the independent or parallel evolution[14]) and other organisms, which assumes that viruses appeared at the same time as the most primitive organisms.

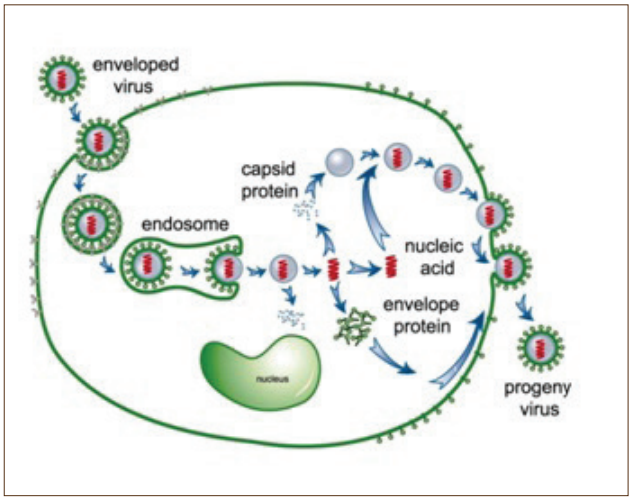

Figure 2. Pictorial Description of Viral Life Cycle

Effective vaccines have led, or might lead, to the eradication of important viral pathogens, such as smallpox, polio, measles, mumps and rubella.[21] In the past few years there have been major shortages of vaccines to treat other diseases like Measles, Hepatitis B, Influenza type A and type B.[22] Viruses present a larger therapeutic challenge since their discovery till date than bacteria may be due to their mode of replication, genetic diversity and because of this now viruses continue to be the major cause of infectious diseases which we cannot treat.[21,23] As a result of this, new strains of viruses constantly emerge. Epidemiological and ecological processes that shape their genetic diversity may be predicted due to the rapid rate of evolutionary change in RNA viruses.[24] Till date scientists so far have only explored <1% of the estimated viral diversity.[2] Development of effective vaccines is the conventional approach to the control of viral diseases. Though it is ideal option but this is not always feasible.

In the following discussion some deadly viral infections are discussed with the important facts. The Disease prevalence and related deaths are mentioned with the most possible updates of numerical figures. The mentioned figures clearly indicates itself threats of viral diseases all over the world.

3. HIV-AIDS

Amongst the hazardous viral infections to the humans, retroviral infection especially by Human Immunodeficiency Virus (HIV) infection, Genus *Lentivirus* of family

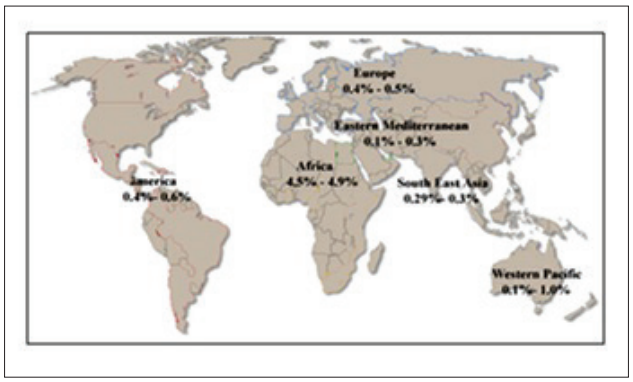

Figure 3. Prevalence of HIV Virus

Retroviridae [25] which is a major concern in the present world and remains as challenging to medical as well drug researchers. The most advanced stage of HIV infection is Acquired Immunodeficiency Syndrome (AIDS) which can take 10-15 years to develop.[26, 27] This stage is defined by the development of certain cancers, infections, or other severe clinical manifestations. Almost ending up 30 years after the causative agent of Acquired Immunodeficiency Syndrome (AIDS) was specifically framed independently by Luc Montagnier and Robert Gallo in the 20 May 1983 edition of Science[28, 29], till date there is unsuccessful battle going to control HIV-AIDS with uncertain hope for successive treatment which will change the scenario of this virus for life threatening to curative viral infection. Since the beginning of the epidemic, HIV virus have infected more than 60 million people and approximately 30 million AIDS related deaths.[30] The reported figures in 2011 for People Living with HIV/ AIDS (PLHA) were 34.2 million.[31] In 2010 for new infections the figure was 2.7 million, and for AIDS-related deaths worldwide was 1.8 million.[32] Sub-Saharan Africa shares more than half of volume of PLHA and almost over 60% of patients were form this region.[31] Demographically India ranks second in the world, and has also the third largest number of people living with HIV/ AIDS (Figure 3).[33] As per the interim HIV estimate of 2008-09, there were an estimated 2.27 million PLHA in India.[34] The HIV prevalence rate in the country is in between 0.29-0.3 % and most common route of transmission is through heterosexual practices with different partners. However in the north-eastern region, Intravenous Drug user (IVD Users) is the major cause for the epidemic spread of infection.

Although there is large patient population worldwide for HIV, only limited options for treatment is available for this infection. Since from approval of first antiretroviral drug, zidovudine in 1987, till date around 20 drugs are used against this virus none of these found significantly effective. Even in the third decade after discovery of viral infection the researchers are unanswered to the vaccine and further there is concern for cost of treatment and safety on prolong use of present drugs. There is large investment done on treatment for HIV. Some charitable trusts also generated large amount of funds at local and international levels to reduce burden related to cost of treatment. Simultaneously there is huge investment is going in research for novel treatment and vaccine research. Vaccine research is yet waiting to come up with success story clearing all phases of clinical trial.

4. HEPATITIS

Hepatitis is a general term for the clinical conditions like inflammation of the liver and may lead by several mechanisms, including infectious agents. Hepatitis Virus can be classified into variety of different sub species such as hepatitis A, B, C, D and E.[35] Potentially life-threatening liver infection is caused by Hepatitis B and Hepatitis C virus. It leads to chronic liver disease and puts people at high risk of death may due to either liver cirrhosis or liver cancer. It is known that humans are the only reservoir of HBV.[36] Percutaneous and permucosal exposure to infected blood and other body fluids, mainly semen and vaginal fluid is the most common mode of virus transmission.

The worldwide spread of the hepatitis viral infection (figure 4) is estimated to >2 billion. Of these, approximately 360 million patients are chronically infected and at risk of serious illness and death, mainly from liver cirrhosis and hepatocellular carcinoma (HCC).[37] The incubation period of HBV is 75 days on average, but may vary from about 30 days to 180 days.[38] From the figures for the year 2000, it was estimated that the number of deaths from HBV-related diseases was at about 6,00,000 per year worldwide. In India, HBsAg prevalence among general population ranges from 2% to 8%, falling India in intermediate HBV endemicity zone of WHO and the number of HBV carriers is estimated

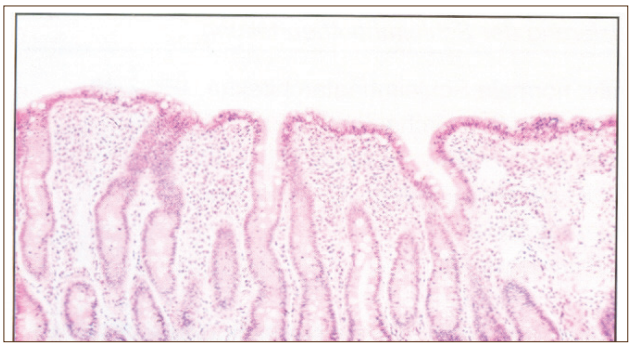

Figure 4- Prevalence of Hepatitis Virus

to be 20-50 million, forming the second largest global pool of chronic HBV infections.[39] The global scale incidence of Hepatitis C Virus (HCV) is not well known[40]; as acute infection is generally asymptomatic that's why most of the patients do not know they are infected with such virus. Reported cases of HCV are as many as 2 to 4 million persons may be chronically infected in the United States, 5 to 10 million in Europe, 1,50,000 new cases occur annually in the US and in Western Europe, 12 million in India and about 350,000 in Japan.[41] As per WHO estimation, about 3% of the world's population has been infected with HCV and further there are about 170 million chronic carriers who are at risk of developing liver cirrhosis and/or liver cancer.

As like HIV, hepatitis does not have hurdles for treatment. Though there is not any finite treatment and successive antiviral drug is available for infection of hepatitis but vaccine for prevention was discovered many years back. Now even hepatitis vaccine is included in regular vaccine program for infants. There is option for interferon both conventional as well as PEG interferon are available for treatment with finite treatment duration and are much safer than antiviral drugs belonging to nucleoside analogues or

protease inhibitor class and current antiviral therapies are usually unable to achieve sustained off-treatment responses and eradicate the infection. But as similar with HIV cost for treatment with interferon in hepatitis is also a major concern. Further hepatitis infection in most time is asymptomatic and thus remains challenging for early detection. Yet its management is more daunting when infection often coexists with other comorbidities, adding further complexity to clinical decision-making. At the community level there also a need to raise awareness about the infection and made them aware to get vaccinated on regular basis.

5. INFLUENZA

Influenza is an easily spreading contagious acute viral infection. Influenza infection is almost circulating worldwide affecting in all age group. It is caused by the influenza virus, which can be spread by coughing, sneezing, or nasal secretions.[42] Influenza infection is seems to be seasonal and causes annual epidemics that peak during winter in clement regions. Seasonal influenza is classified into three types i.e. seasonal influenza – A, B and C.

Comparing between these types of virus, epidemic as well as pandemic of influenza A virus is greater than that of influenza B virus which is responsible for severe epidemics. This same fact reflects in the study conducted by World Health Organization (WHO) and National Respiratory and Enteric Virus Surveillance System (NREVSS) in 2nd October, 2011–11th February, 2012, 90% were positive for influenza A viruses, and 10% were positive for influenza B viruses.[43] Influenza A viruses comprises a large variety of antigenically distinct subtypes, with different combinations of virus surface glycoproteins namely haemagglutinin (HA) and neuraminidase (NA), that replicate asymptomatically.[44] Influenza A viruses are further sub divided into antigenically distinct subtypes according to different combinations of virus surface proteins, 15HA and 9NA subtypes.[45] Among many subtypes of influenza A viruses, only few subtypes are known to have established in humans. On the basis of reported cases of Influenza Type C virus infection we can say that the infection may occurs much less frequently than A and B. Illnesses caused by influenza virus results in hospitalizations and further leads in mortality mainly among high-risk groups (the very young, elderly or chronically ill). Worldwide, these seasonal epidemics catch about 3 to 5 million cases of severe illness, and about 2,50,000 to 5,00,000 deaths.[46] Influenza is life threatening for higher risk populations (mentioned earlier), and viral infection may leads to severe illnesses and deaths also.

Influenza pandemics are controlled worldwide to some extent with successive use of vaccines. Influenza vaccine is also mandatory in National Immunization Schedule of many countries. In past few years there is gap between need and supply for influenza virus in many parts of world. Besides control of influenza infection a large number of influenza related deaths were reported every year. After infection with virus some antiviral drugs are also available for treatment of influenza infection. New studies highlight the emergence of oseltamivir resistance in influenza A H1N1 viruses. However, oseltamivir-resistant strains were noted worldwide during the 2007–2008 influenza season. Thus action should be taken before emergence of next pandemic of influenza with such kind of resistance.

6. MEASLES

Measles virus belongs to the paramyxovirus family of the genus Morbillivirus. Measles is an infection of the respiratory system and the measles virus normally grows in the cells that line the back of the throat and lungs and can be accurately diagnosed clinically.

Measles is an acute viral illness characterized by a cough, runny nose, sore throat, red eyes, a rash that begins behind the ears and a high temperature. One in 15 children who contact measles develops serious complications which can include bronchitis, pneumonia, convulsions and encephalitis.[47] Measles is a human disease and is not well known to occur in animals.[48] Even though a safe and cost-effective vaccine is available; measles requires attention as it is leading causes of death among young children. The disease is as severe as those handfuls of diseases which contribute 90% of infectious disease deaths.[49]

In the period of 2001 to 2011 more than 1 billion children of age group between 9 months to 14 years of high risk countries were vaccinated against the measles disease. Though Accelerated immunization activities with measles vaccine resulted in a 74% drop in measles deaths from 5,35,300 in 2000 to 1,39,300 in 2010 worldwide, still as per estimations in 2010 nearly 1,39,300 measles related deaths occurred globally, on the other way we can say nearly 380 deaths every day or 15 deaths occurs every hour worldwide.[50] Out of reported measles related deaths more than 95% of deaths occurred in low income countries with weak healthcare infrastructure facilities. As per report of Times of India, published in 24th April, 2012; in Indian 2010 recorded nearly 30,000 new cases of measles, and recorded 65,500 deaths contributing 47% of global measles deaths.[51]

Measles has a severe effect on the nutritional status of a child: well-nourished children who are otherwise healthy lose weight when they have the measles, while malnourished children become seriously ill. Except developed countries, in many developing countries where conditions of poor nutrition, poor sanitation, and lack of adequate health care are common, measles mortality rates are considerably higher, especially among children. There is no specific treatment for measles. Most patients with uncomplicated measles will recover with rest and supportive treatment. The only safe and effective way is to use of vaccines against measles. With availability of safer and effective vaccine there are many obstacles to eradicate viral infection and have. Present situation needs a novel virus specific antiviral drugs which can imply as supportive treatment for the infected children as well as adults.

7. RUBELLA

The rubella virus is an enveloped single stranded RNA virus with a single serotype belonging to family togavirus and genus Rubivirus.[52] Rubella is an acute, contagious, usually mild viral infection affecting mostly to children and young adults. After infection replication of the virus is thought to occur in the nasopharynx and regional lymph

nodes. While the illness is generally mild in children, Congenital rubella syndrome (CRS) is due to rubella infection tends to serious consequences in pregnant women and when a pregnant woman is infected with the rubella virus early in pregnancy, she has a 90% chance of passing the virus on to her fetus causing miscarriage, stillbirth or severe birth defects (CRS).[53] The other major problems associated with CRS include deafness, blindness, heart disease, and mental retardation.[54]

Infants with CRS may excrete the virus for 1 year or even for more time period. Immediate after exposure to virus it spreads throughout the body in about 5-7 days and usually symptoms appear 2 to 3 weeks after exposure. Humans are the only known host and transmission is by respiratory droplets. Viral replication occurs in the nasopharyngeal mucosa and local lymph nodes. The incubation period ranges from 12 to 23 days with an average of 18 days. Worldwide around 1,10,000 births are reported with CRS each year. Comprehensive evidence about the true burden of CRS in India is not available as no systematic review or nation-wide cohort study is available to address disease burden or prevalence of CRS. Yet there is lack of virus specific treatment for rubella but the disease can be preventable by vaccination only.[55] The initial 1–5 days after the appearance of the rash are usually most infectious period.

There is no specific treatment for Rubella; however, management is a matter of responding to symptoms to diminish discomfort. Treatment of newly born babies is focused on management of the complications.

8. DISCUSSION

Since from the discovery of viruses the viral infections caused due to different species hampered the social life/community on higher degree. The number of deaths put together for all viral infectious diseases is very high. The only infectious diseases discussed above count together for more than 50% total deaths caused worldwide. In view of the spread of infections most viral infections are growing on consistent rates like retroviral infections, viral hepatitis; while some of the infections are seasonal like Influenza, Chandipura. With the development of science viral infections can be prevented by the use of vaccines. In some of the viral infections vaccines prove to be very effective option but this can be implemented as a prophylactic option for certain viral infections. Scientists still unable to withstand by mean of vaccines or drugs against some serious viral infections. We can say that vaccines are as safe and effective option for viral infection but not true for all viruses. As viruses success to invade in to host cells and thus replicate there gradually it is difficult then to manage the infection. Though numbers of antiviral drug are present in market for treatment, they are not surely eradicating the viral infection from host cells as antibiotics do for bacteria. Instead antiviral drug decreases certain log concentrations of viruses in host and this suppress the symptoms. Thus today community from all over the world demands for such effective antiviral drug which can completely eradicates the infection but yet is the major challenge for researchers working in this field.

The development of the vaccines and the drugs is not only the option for this situation but the step next to this is the sufficient supply of the vaccines and drugs to all levels of the community. With the present condition of countries like India where the problems of continuous increasing population, large groups of financially weak societies with inheriting illiteracy are always at their peak. In the present days though WHO declares India as polio free but still there is hidden threat of reemergence of the viral infection and this may because of the healthcare facilities present in the country as compare to western country. Somewhere all these conditions count for the spread of the infectious diseases and leads to unhealthy society. In the same way if considered for PLHIV, India stands at 3rd rank worldwide, for viral hepatitis India is 2nd largest global pool. Similar way India shares almost half count of the numbers of total deaths caused worldwide due to measles.

9. CONCLUSION

In view of the present conditions and the threat of the viral infections worldwide, it is now important to upgrade the existing facilities and fulfill the demand. Further in the existing regimens present to treat various viral infections, no drugs is effective for complete eradication of viral infections. So there is urgent need of development of new antiviral drugs which are safe and effective as compare to present treatment.

REFERENCES

1. Randles J, Ogle H. Viruses and viroids as agents of plant disease. Plant Pathogens and Plant Diseases. Brown JF, Ogle HJ editor. Australia: Rockvale Publication: 1997. p. 104-26.
2. Wobus CE, Nguyen TH. Viruses are everywhere — what do we do? Current Opinion in Virology 2012; 2:60–2.
3. Liu S, Vijayendran D, Bonning BC. Next generation sequencing technologies for insect virus discovery. Viruses 2011; 3:1849-69.
4. Virology blog: Racaniello V. Discovery of viruses. 23rd December 2008. Available from: http://www.virology.ws/2008/12/23/discovery-of-viruses. Assessed 09 August 2012.
5. Koonin EV, Senkevich TG, Dolja VV. The ancient virus world and evolution of cells. Biology Direct 2006; 1:29.
6. Rhodes AJ. Recent advances in virus infections: the new era in virology. British Medical Journal. London Saturday April 9 1960; 1071-77
7. Bandea CI. The origin and evolution of viruses as molecular organisms. Nature Preceding. hdl: 10101/npre. 2009. 3886.1: Posted 21 Oct 2009.
8. Gelderblom HR. Structure and classification of viruses. In: Baron, S., editor. Medical Microbiology. 4th edition. 1996, University of Texas Medical Branch at Galveston. Available from: http://www.ncbi.nlm.nih.gov/books/NBK8174/. Assessed on August, 2012.
9. Leiman PG, Kanamaru S, Mesyanzhinov VV, Arisaka F, Rossmann MG. Structure and morphogenesis of bacteriophage T4. CMLS Cellular and Molecular Life Sciences 2003; 60: 2356–70.
10. Villarreal LP. Are Viruses Alive? Scientific American, Inc.102 Scientific American December 2004. Available on free database from: w w w. s c i a m . c o or available on free database from: mhttp://scidiv.bellevuecollege.edu/bron/Bio%20211%20Web%20S09/password%20211/VirusesAlive%20Villarreal%2004.pdf
11. Forterre P. New hypotheses about the origins of viruses, prokaryotes, and eukaryotes. Frontiers of Life, Van TT, Mounolou JK, Shneider J, Mc Kay C. editor Editions Frontieres. Gif-sur-Yvette Cedex, France 1992; 221–34.
12. Forterre P. The origin of viruses and their possible roles in major evolutionary transitions. Virus Res 2006; 117(1): 5-16.
13. Carter JB. Saunders VA. Viruses and their importance. Virology: Principles and Applications. John Wiley & Sons, Ltd. 2007; 1-8.
14. Bubanovic I. Najman S. Andjelkovic Z. Origin and evolution of viruses: Escaped DNA/RNA sequences as evolutionary accelerators and natural biological weapons. Medical Hypotheses 2005; 65: 868–72.

15. Poole1 AM. Penny D. Evaluating hypotheses for the origin of eukaryotes. BioEssays 2006; 29:74–84.
16. Mahy BWJ, Van Regenmortel MHV. Desk Encyclopaedia of General Virology. Academic Press, Jordan Hill, Oxford, UK 2010; 1-107
17. Huang CR, Lo SJ. Evolution and Diversity of the Human Hepatitis D Virus Genome. Advances in Bioinformatics Volume 2010; Article ID 323654, 1-9.
18. Yozwaik N. How did viruses evolve from a universal common ancestor? Ask A Scientist. HHMI bulletin. May 2011; 45.
19. Makałowska I, Rogozin IB, Makałowski W. Genome Evolution. Advances in Bioinformatics Volume 2010; Article ID 643701: 1-2.
20. Krupovic M, Ravantti JJ, Bamford DH. Geminiviruses: a tale of a plasmid becoming a virus. BMC Evolutionary Biology 2009; 9:112.
21. Fraser CM. The Merck Veterinary Manual. Pharmacology: Antiviral Agents and Biologic Response Modifiers: Introduction. Available from www.merckvetmanual.com/mvm/index. Assessed on 10 August, 2012.
22. Jain S, Vyas RK, Pandit P, Vyas S. A review on fate of antiviral drugs in environment and detection techniques. International Journal of Environmental Sciences 2011; 1(7): 1526-41.
23. English JP. The chemotherapy of infectious disease, 1909-1959. Journal of Chemical Education. April 1960; 37(4) : 172-77.
24. Holmes EC. Evolutionary history and phylogeography of human viruses. Annual Review of Microbiology. 2008; 62: 307–28.
25. Levy JA. Discovery, structure, heterogeneity, and origins of HIV. HIV and the pathogenesis of AIDS. Third edition, Washington, D.C: ASM Press, 2007: 1-26.
26. UNAIDS database. Fast facts about HIV. UNAIDS: Joint United Nations Programme on HIV/ AIDS. Available on http://www.unaids.org. Assessed on August, 2012.
27. Scherer E, Douek D, Mc Michael A. 25 years of HIV research on virology, virus restriction, immunepathogenesis, genes and vaccines. British Society for Immunology, Clinical and Experimental Immunology 2008; 154: 6–14.
28. Montagnier L, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, D, et al. Isolation of a T-Lymphotropic retrovirus from a patient at risk for Acquired Immune Deficiency Syndrome (AIDS). Science, New Series, May 20, 1983; Vol. 220, No. 4599: 868-71.
29. Weiss RA. Special Anniversary Review: Twenty-five years of human immunodeficiency virus research: successes and challenges. British Society for Immunology, Clinical and Experimental Immunology 2008; 152: 201–210.
30. World Health Organization Data Base: Global Health Observatory (GHO)–HIV/AIDS. World Health Organization 2012. Available on www.who.int. Assessed on August 2012.
31. Media centre: HIV/AIDS Fact sheet No 360, July 2012. World Health Organization 2012. Available from http://www.who.int/mediacentre/factsheets/fs360/en/index.html. Assessed on August 2012.
32. Global Health Observatory (GHO): World health statistics 2012. World Health Organization 2012. Available from www.who.int/gho/publications/world_health_statistics/2012/en/. Assessed on August 2012.
33. Annual Report 2010-11. Department of AIDS Control National AIDS Control Organisation Ministry of Health & Family Welfare Government of India. Available from http:\\nacoonline.org. A s - sessed on August 2012.
34. National Aids Control Programme: Response to the HIV Epidemic in India. Department of AIDS Control National AIDS Control Organisation Ministry of Health & Family Welfare Government of India. Available on http:\\nacoonline.org. Assessed on August 2012.
35. Zuckerman AJ. Hepatitis Viruses. In: Baron, S., editor. Medical Microbiology. 4th edition. 1996, University of Texas Medical Branch at Galveston. Available in http://www.ncbi.nlm.nih.gov. Assessed on August, 2012.
36. Epidemiology and Prevention of Vaccine-Preventable Diseases. The Pink Book: Course Textbook. 12th Edition, (2 pt) 115-138.
37. Hepatitis B Fact sheet No 204, July 2012. World Health Organization 2012. Available from: http://www.who.int/mediacentre/factsheets/fs204/en/index.html. Assessed on August 2012.
38. Weekly epidemiological record. 2 October, 2009, 84th year, No. 40. 2009; 84: 405–420.
39. Datta S. An overview of molecular epidemiology of hepatitis B virus (HBV) in India. Virology Journal 2008, 5:156-167.
40. Averhoff FM, Glass N, Holtzman D. Global Burden of Hepatitis C: Considerations for Healthcare Providers in the United States. Clinical Infectious Diseases 2012; 55(S1): S10–15.
41. Global Alert and Response (GAR). Hepatitis C- Surveillance and Control. Available on http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index4. Assessed on Aug 2012.
42. Influenza Vaccine Information Statement. U.S Department of Health and Human Services- Centre for Disease Control and Prevention. Available from: www.cdc.gov/vaccinesafety/Activities/Activities. Assessed on August 2012.
43. Influenza Vaccination Coverage among Pregnant Women — 29 States and New York City, 2009–10 Season. Centers for Disease Control and Prevention- Morbidity and Mortality Weekly Report (MMWR). Weekly / Vol. 61 / No. 7 February 24, 2012.
44. Rao BL. Epidemiology and control of influenza. The National Medical Journal of India 2003. 16(3): 143-149.
45. Hay AJ, Gregory V, Douglas AR, Lin YP. The evolution of human influenza virus. Philosophical Transactions of the Royal Society. Series B: Biological Sciences. 2001. 356: 1861-70.
46. Media centre Influenza (Seasonal) Fact sheet No. 211, April 2009. World Health Organization 2012. Available from http://www.who.int/mediacentre/factsheets/fs211/en/index.html. Assessed on August 2012.
47. Measles, Mumps & Rubella- Frequently Asked Questions. National Immunization Advisory Committee Royal College of Physicians of Ireland. March 2002.
48. Measles Fact Sheet. Epidemiological Unit. Ministry of Healthcare and Nutrition. 231, De Saram Place, Colombo 10.
49. Dr. Brundtland GH. Six diseases cause 90% of infectious disease deaths. Removing Obstacles to Healthy Development. WHO Report on Infectious Diseases. World Health Organization 1999.
50. Measles Fact sheet No. 286. April 2012. World Health Organization 2012. Available from: http://www.who.int/mediacentre/factsheets/fs286/en/index.html. Assessed on August 2012.
51. Sinha K. Times of India report: 47% of global measles deaths in India. Apr 24, 2012.
52. Atkinson W. Hamborsky J. Wolfe S. eds. Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. 12th ed., second printing. Washington DC: Public Health Foundation 2012: 275-90.
53. Rubella Fact sheet No. 367. July 2012. World Health Organization 2012. Assessed on August 2012.
54. The epidemiologic and clinical basis of rubella surveillance. Measles and Rubella Surveillance and Outbreak Investigation Guidelines. World Health Organization, Regional Office for South-East Asia. 2009. 57-64.
55. Dewan P, Gupta P. Burden of Congenital Rubella Syndrome (CRS) in India. Indian Pediatrics Volume 49. May 16, 2012. 377-99.