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# Emerging Viral Diseases in India: A Review

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**ABSTRACT**

The incidence of emerging infectious diseases in humans has increased within the recent past or threatens to increase in the near future. Over 30 new infectious agents have been detected worldwide in the last three decades; 60 per cent of these are of zoonotic origin. Developing countries such as India suffer disproportionately from the burden of infectious diseases given the confluence of existing environmental, socio-economic, and demographic factors. In the recent past, India has seen outbreaks of eight organisms of emerging and re-emerging diseases in various parts of the country, six of these are of zoonotic origin. Prevention and control of emerging infectious diseases will increasingly require the application of sophisticated epidemiologic and molecular biologic technologies, changes in human behaviour, a national policy on early detection of and rapid response to emerging infections and a plan of action. WHO has made several recommendations for national response mechanisms. Many of these are in various stages of implementation in India.

**Key words :** Ebola, dengue, chikunguniya, swine flu.

## INTRODUCTION

India the second most populous country in the world is at risk due to viral diseases that emerging as fast as possible .most of the organisms are zoonotic in origin.

Over 30 new infectious agents have been described worldwide in last two decades.InIndia due to existing environmental, socioeconomic and demographic factors the emergence of viral infections are increased.Epidemic and endemic are the other causes for these viruses.

It posed a serious threat to global health security, the health system capacities to cope where health workers were at risk and the stability and growth of economics. There are many viral diseases that cause infection the most common viral infections that emerging in India are influenza, chikunguniya, ebola, dengue,nipah virus.

More recently cases of H1N1 influenza was reported in mexico in march 2009,then followed by spread to united states and to India by September.

This was an example that highlights the risks and need to improve the alertness at national and international levels for future pandemics. It is clear that, new pathogens particularly viruses are likely to continue to emerge and spread across countries for a variety of reasons and challenge public health as never before. These will represent a serious burden, causing untold morbidity and mortality, disrupting trade and travel, and negatively affecting the economy.

This paper provides an overview of emerging infections in India, their determinants, in detail.

**History and epidemiology of the diseases**

Ebola virus is predominantly a zoonotic virus. It was first found as the etiologic agent in the year 1976 in the cases of hemorrhagic fevers in Zaire and Sudan. It causedan epidemic in these areas with a fatality rate of around 50 to 90%. This epidemic was attributed to interhuman spread in hospital settings with practice of sharing unsterilized needles in these resource limited countries. The next epidemic of Zaire Ebola viral disease (EVD) occurred in 1995. Ever since, intermittent outbreaks have happening in Gabon district between 1995to 2003.

Till recent times around 20 outbreaks have been reported around central Africa with the majority caused by species Zaire ebolavirus. Outside Africa there had been reports of Ebola viral infection in monkeys in Reston region of Virginia in USA in the year 1989 which was concluded to have come through a Philippine exporter.

Recently there has been an outbreak of this infection in West Africa and the CDCas of June 18 2014 has officially reported 528 cases and 337 deaths due to Ebola viraldisease in the three African countries of Guinea, Sierra Leone and Liberia attributingto a 64% of case fatality rate. This has been the largest ever documented outbreak ofthisdisease.Hence there has been increased focus on this infection.

Dengue virus was isolated in Japan in 1943 by inoculation of serum of patients in suckling miceand at Calcutta (now Kolkata) in 1944 from serum samples of US soldiers. The first epidemic of clinical dengue-like illness was recorded in Madras (now Chennai) in 1780 and the first virologically proved epidemic of DF in India occurred in Calcutta and Eastern Coast of India in 1963-1964. The first major epidemic of the DHF occurred in 1953-1954 in Philippines followed by a quick global spread of epidemics of DF/DHF8. DHF was occurring in the adjoining countries but it was absent in India for unknown reasons as all the risk factors were present. The DHF started simmering in various parts of India since 1988. The first major wide spread epidemics of DHF/DSS occurred in India in 1996 involving areas around DelhiandLucknowand then it spread to all over the country.

The epidemiology of dengue fevers in the Indian subcontinent has been very complex and has substantially changed over almost past six decades in terms of prevalent strains, affected geographical locations and severity of disease. The very first reportof existence of dengue fevers in India was way back in 1946. Thereafter, for the next 18 years, there was no significant dengue activity reported anywhere in the country. In 1963-1964, an initial epidemic of dengue fever was reported on the Eastern Coast of India, it spread northwards and reached Delhi in 1967and Kanpur in 1968.

Simultaneously it also involved the southern part of the countryand gradually the whole country was involved with wide spread epidemics followed by endemic/hyperendemic prevalence of all the four serotypes of DV. The epidemiology of dengue virus and its prevalent serotypes has been ever changing. The epidemic at Kanpur during 1968 was due to DV-4and during 1969 epidemic, both DV-2 and DV-4 were isolated. It was completely replaced by DV-2 during 1970 epidemic in the adjoining city of Hardoi. Myers *etal*had reported the presence of DV-3 in patients and *Ae. aegypti*at Vellore during the epidemic of 1966 while during the epidemic of 1968, all the four types of DV were isolated from patients and mosquitoes.

In another study Myers &Varkeyreported an instance of a third attack of DV in one individual. DV-2 was isolated during the epidemics of dengue in urban and rural areas of Gujarat State during 1988 and 1989. Outbreaks of dengue occurred in Rajasthan by DV- 1 and DV-3, Madhya Pradesh by DV-3, Gujarat by DV-2and in Haryana by DV-2. DV-2 was the predominant serotype circulating in northern India, including Delhi, Lucknow and Gwaliorwhile DV-1 was isolated during the 1997 epidemic at Delhi. The phylogenetic analysis by the Molecular Evolutionary Genetics Analysis programme suggests that the 1996 Delhi isolates of DV-2 were genotype IV. The 1967 isolate was similar to a 1957 isolate of DV, from India, and was classified as genotype V.

Human infections caused by Chikungunya virus (CHIKV) were reported for the first time in East Africa some five decades ago in 1952-53 during an epidemic of fever that developed

along the border between Tanzania and Mozambique. This fever was again later described by M. Robinson and W.H.R. Lumsden in 1955

In detail, CHIKV has been reported in the following African countries: Benin, Burundi, Cameroon, Central African Republic, Kenya, Uganda, Malawi, Senegal, Congo, Nigeria, Sudan, Guinea, South Africa, Tanzania, Zimbabwe, Namibia, Comoros, Mayotte, Ghana, Burkina Faso

Mozambique, and Gabon. Most of the CHIKV cases in Asia were reported in India, Sri Lanka, Myanmar, Thailand, Vietnam, Taiwan, Singapore, Cambodia, Pakistan, Laos, Philippines, Malaysia, Indonesia, and East Timor. In the Indian Ocean area CHIKV infections have been recently reported from Seychelles, Madagascar, Mauritius and La Reunion

More recently, the CHIKV diffusion area moved westbound, involving many islands of the Indian Ocean .In particular, between February 2005 and March 2006, CHIKV.

Swine influenza virus which was first isolated from pigs in 1930 in U.S.A., It has been noticed that people who are in close proximity to pigs (for e.g. farmers, pork processors etc.) usually get the infection, thereby causing similar symptoms. The cross-species infections (swine virus to human; human virus to pigs, avian virus to human and pigs) have been found globally. Swine flu strain, causing 2009 pandemic was first seen in Mexico USA.

In 1918 there was an epidemic of “Spanish flu” with a mortality rate of around 2-20%, whereas swine flu or H1N1 has mortality rate of less than 6 %. Although the virus was first discovered in 1930 the disease was not observed much until it came into lime light after the pandemic 2009 which affected almost all countries in the world.

The Nipah virus was first recognized in 1999 during an outbreak among pig farmers in Malaysia. Since then, there have been 12 additional outbreaks, all in South Asia. Fruit bats of the *Pteropodidae*family are the natural hosts for Nipah virus. Evidence shows that geographical distribution of Henipavirus (Nipah and Hendra) overlaps with that of *Pteropus*a high case fatality rate (60-70%) were some of the alarming developments seen in Nipah outbreaks in India (2001) and Bangladesh (2001, 2006)

**Clinical features of diseases**

The incubation period of EVD is around 2 -21 daysafterwhichpatients usually present with nonspecificcomplaints of malaise, fever, chills, myalgia, headache,nausea, vomiting and diarrhea. These complaintsare sudden in onset; the diarrhea usually is bloodyin nature. In light skinned patients around 5th day an erythematous nonitchymaculopapular rash has beenreported which later undergoes desquamation.Bleeding or hemorrhagic manifestations usuallyoccur around the same time. Bleeding from mucosa,hemoptysis, hematemesis, hematuria, ecchymosesetc have been reported. Edema of face, scrotum and neck has also been seen. In severe cases EVD can lead to hepatic failure, renal failure, MODS (multiorgandysfunction syndrome), pancreatitis, shock and death. In mild cases fever undergoes defervesence around 10-12 days.

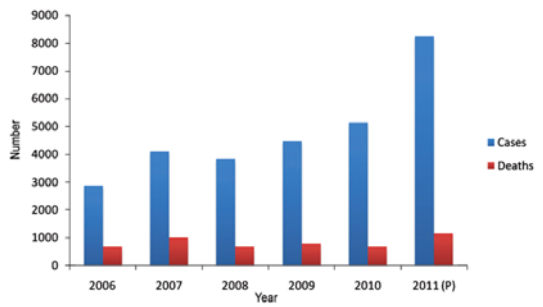
Encephalopathy, acute motor weakness, seizures, neuritis, GuillainBarre syndrome, hypokalemic paralysis acute viral myositis, acute encephalitisAcute liver failure, significant mortality, hepatic encephalopathy, hepatomegaly epistaxis, jaundice and petechial rashesAcute myositis, pure motor quadriplegiaAcute reversible cardiac insult, sinoatrial block and atrioventricular dissociation Abnormal immune response leading to systemic lupus erythematosusUnilateral blurring of inferior visual fieldIncrease in oxidative stress, significantly elevated PCOs and low PBSH group levelsRenal dysfunction, acute kidney injury.Lower gastrointestinal bleeding and acute inflammatory colitisMaculopapular/morbilliformeruption followed by ecchymotic, petechial, and macular/ scarlatini formeruption Confluent erythema, morbilliform eruptions, and haemorrhagiclesionsYoung child developed Kawasaki disease later in disease.Bone marrow haemophagocytosis associated with nasal bleeding and pancytopeniaChikungunya fever is an acute illness characterized by a sudden onset of high fever, rash and joint pain. The most significant symptom of CHIKV-related disease consists of a painful arthralgia that occurs in almost

100% of patients. Most infections completely resolve within weeks but there are reported cases of CHIKV-induced arthralgia lasting for months, or even for years, in the form of recurrent or persistent episodes.Swine flu virus causes clinical symptoms in human beings which are analogous to other influenza viruses and are further categorized into following: Common symptoms are fever (100 F or greater), cough, nasal secretion, fatigue, and headache with fatigue. Rare symptoms include nausea, vomiting, diarrhea and sometimes collateral tissue damage. In severe cases patients can have severe respiratory symptoms there by needing respiratory support. Complications: pneumonia due to secondary bacterial infection, seizures, and rarely death.

**Diagnosis**

The initial diagnosis is usually based on clinicalassessment. Blood tests for definitive diagnosisand confirmation are usually done at national andinternational reference laboratories, which shouldbe contacted immediately in case of suspicion, whoadvice on proper sample collection and transport.A biosafety level 4 laboratory is only authorizedto conduct these tests. These precautions are veryessential because of the high infectivity of the virusand its potential of spread via medical facilities ifappropriate measures are not taken.Laboratory diagnosis of Ebola virus is arrived atby two ways, first by measurement of host-specificimmune responses toinfection and second by detectionof viral particles or particle components in infectedindividuals.Acute infection is diagnosed by RT PCR tests orELISA to detect viral antigens, these tests can bepositive from day 3 to day 15 of infection.Antibodies are tested either by direct IgG and IgMELISA or IgM capture ELISA, IgM antibodies appearin blood by day 3 and disappear by 30 to 150 days.WhileIgG antibodies appear by day 6 and canremain in blood for many years. IgM or rising IgGtitreconstitutes a strong presumptive diagnosis.14All the above tests are done on materials that havebeen rendered noninfectious prior to testing.Skin biopsy for detection has been advised on postmortem samples for confirmation of EVD.Diagnosis of DV infection is routinely done by demonstration of anti DV IgM antibodies or by NS-1 antigen in patients' serum depending upon day of illness using ELISA kits (prepared by National Institute of Virology, Pune) and commercial kits. Molecular methods (reverse transcriptase PCR) are being increasingly used in diagnosis of DV infection. A single tube nested PCR for detection and serotyping of DV was developed and used for detection of co-infection by two viruses. DV isolation in tissue culture cells and its sequencing is also being done.The laboratory diagnosis of CHIKV infection is routinely achievable by different methods, including the isolation of the virus in cell culture from plasma or serum; the detection of the viral RNA by RT-PCRin serum; and the evaluation of the CHIKV-specific serologic antibody response (IgM and/or IgG antibody detection or identification of an antibody mediated viral neutralizing activity in serum). Virus isolation is based on inoculation of the biological sample in cell cultures, derived either from mosquitoes or from mammals. As an alternative, the specimen for CHIKV detection can be inoculated into suckling mice. This last method is, however, labour intensive and time-consuming. To detect the presence of viral RNA, several real-time RT-PCR protocols, targeting the *nsp1* or *E1* gene, have been developed. Molecular tests are capable of detecting the viral RNA only during the viremic phase in patients, which usually lasts from day 0 to day 6 after the clinical onset. Parola and colleagues,analysed serum samples from four infected travellers returning from the Indian Ocean islands by using a quantitative real-time RT-PCR-based method and detected a viral load up to 109 copies/ml in one case; these findings suggested that the veremia can reach very high concentration during the symptomatic phase of CHIKV infection. Such high levels of viremia are uncommon in other arthropod-borne diseases such as dengue fever and West Nile disease. No clear information is presently available about the viral load that is present in serum during the pre-symptomatic stage of infection, which likely lasts for some days before the clinical onset. CHIKV specific IgM and IgG antibodies are detectable in plasma and serum samples from acutely infected and convalescent patients by the following classic serological methods: inhibition of the haemagglutination, complement fixation, immunofluorescence (IIF) and immunoenzymatic assays (ELISA). The IgM specific response against CHIKV is detectable starting from two to six days after the onset of symptoms by ELISA and IIF, and could persist for several weeks up to

three months. The IgG antibodies are present in sera from convalescent stage patients and usually persist for several years. All the above reported serological methods are highly sensitive but only moderately specific: this phenomenon is mainly due to the antigenic cross-reactivity between CHIKV and other arboviruses such as Dengue virus, o'nyong-nyong virus, Sindbis virus, and many others. Furthermore, as the clinical symptoms of CHIKV infection resemble those of several other febrile arthropod-borne infections (mainly Dengue).Confirmation methods is required either in patients living in endemic countries or in travellers returning from tropical areas that were detected as IgM or IgG positive by standard serological tests. Confirmation is generally achieved by performing a plaque neutralization test (PRNT) *in vitro*: this assay is time-consuming and labor intensive and can be routinely performed by third level laboratories that act as reference structures. Up to now, in-house ELISA and IIF tests were mainly used for CHIKV diagnosis. Recently, some commercially available serologic assays, including IIF and ELISA, were developed and their sensitivity and specificity values were evaluated and assessed.It is recommended that only hospitalized patients undergo the tests from reference labs. Swine flu can be diagnosed by two approaches: Presumptive diagnosis: it can be made through patient's history along with clinical symptoms Definitive diagnosis: it is made through laboratory investigations which are as follows Quick tests (for example, nasopharyngeal swab sample) are done to see if the patient is infected with influenza A or B virus. The test can be negative (no flu infection) or positive for type A and B. If the test is positive for type B, the flu is not likely to be swine flu (H1N1) and if it is positive for type A, then the person could have a predictable flu strain or swine flu (H1N1).Though these tests are quick but are less precise and non-specific for H1N1.Swine flu (H1N1) is definitively diagnosed by detecting the particular antigens associated with the virus type. These tests are done in a specialized laboratory. Because of the large number of novel H1N1 swine flu cases that occurred in the 2009-2010 flu season (the vast majority of flu cases [about 95%-99%] were due to novel H1N1 flu viruses), it was recommended that only hospitalized patients' flu virus strains should be sent to reference labs for identification. Rapid antigen testing (RIDT), DFA testing, viral culture, and molecular testing (RT-PCR) are used for its diagnosis.




**Complying with international health regulations (IHR)**

In 2005, the 194 member countries which are considered as States Parties passed the International Health Regulations known as IHR (2005). As a legal instrument, the aim is to ensure public health through the prevention of disease spread across borders, with limited interference to international traffic and trade. In order to do so, IHR (2005) requires all countries to assess their surveillance and response capacities, and to ensure that the core capacities are built by 2012. At the time of the SARS outbreak, countries were only required to notify WHO of yellow fever, cholera and plague outbreaks under the IHR. After SARS, it was clear that the rules needed to be updated considering the increase in international travel and trade, and emergence and re-emergence of new international disease threats. A revised version was developed and in May 2005 it was approved by the World Health Assembly. The purpose and scope of the new regulations are not limited to any specific diseases or manner of transmission, but rather address illness or medical condition, irrespective of origin or source, that presents or could present significant harm to humans.As one of the signatories, India has been implementing various provisions of the IHR to enhance national and thereby global public health security by preventing and responding to acute public health risks that have the potential to cross borders and may constitute a potential threat to other countries. NCDC is the focal point for IHR in India and efforts are being made to strengthen core capacities needed under IHR (2005). In recent years, the

epidemic disease act 1897 has been invoked by various States of India to tackle the challenges of communicable diseases like pandemic HINI influenza.

**Strengthening of laboratory and networks**

The National Institute of Communicable Diseases (NICD) has been upgraded to National Centre for Disease Control (NCDC) as a centre of excellence with responsibility for enhanced capabilities for rapid response and laboratory based surveillance of communicable diseases. Under the IDSP, 50 district public health laboratories are being strengthened all over the country. Alongside, a network of referral laboratories utilizing the services of existing functional laboratories in the nine States is being established. These include existing laboratories in microbiology departments of medical colleges and other large institutions for the aetiological diagnosis of outbreaks. This network would allow access to quality public health laboratory services for selected linked districts

**Information sharing and partnerships**

The recent pandemic HINI influenza and avian influenza brought the international scientific community together showing the importance of effective partnerships in combating emerging infections. Under the international health regulations, national focal points are required to work closely with relevant ministries in timely identification of extraordinary public health events. As the national focal point for International Health Regulations (IHR) in India, the NCDC is in the process of identifying and partnering with other relevant ministries in identification of public health emergencies of internatonal concern (PHEIC).

## CONCLUSION

For a country of size and population of India, the emerging infections remain a real challenge. A meaningful response must approach the problem at the systems level. A comprehensive national strategy on infectious diseases addressing the challenges of emerging and re-emerging infections cutting across all relevant sectors, both governmental and non-governmental, should be in place. Identification of national centres of excellence and their capacity building is of critical importance. These centres of excellence should be encouraged to develop networking and partnerships between public health organizations to improve their individual scientific capacity, share best practices and expand collective knowledge base. Concerted efforts are also needed to develop advanced countermeasures such as surveillance tools, diagnostic tests, vaccines and therapeutics through basic, translational and applied research. Sensitive rapid response mechanisms at various levels of health service are the cornerstone to detect public health threats and respond quickly enough to protect valuable human lives. National commitment and comprehensive efforts are necessary at all levels of health services in order to meet the threat of emerging and re-emerging infections.

## REFERENCES

1. Bhatia1. R, Narain JP, Plianbangchang S. Emerging infectious diseases in East and South-East Asia. In: Detels R, Sullivan SG, Tan CC, editors. *Public health in East and South-eastAsia*. Berkeley, USA: University of California Press; p. 43-78 (2012).
2. Fauci AS. Infectious diseases: considerations for the 21st 2. century. *Clin Infect Dis*; **32:** 675-85 (2001)
3. Taylor LH, Latham SM, Woolhouse ME. Risk factors for 3. human disease emergence. *Philos Trans R SocLond B BiolSci*; **356** : 983-9 (2001)
4. Morbidity and Mortality Weekly Report; **63**:25 (2014)
5. Feldmann H, Geisbert TW. Ebola haemorrhagic fever. *Lancet*; **377**:849–862 (2011).
6. Whitehorn J, Farrar J. Dengue. 1. *Br Med Bull*; **95:** 161-73 (2010).
7. Robinson MC, An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952-53. I Trans R Soc Trop Med Hyg **49**: 28–32 (1955).

8. Lahariya, C and Pradhan SK, Emergence of chikungunya virus in Indian subcontinent after 32 years: a review. *J Vector Borne Dis* **43**: 151–160 (2006).
9. Guzman MG, Kouri G. Dengue: an update. *Lancet Infect Dis;* **2**: 33-42 (2002).
10. Smith AW, Chen LH, Massad E, Wilson ME. Threat of dengue to blood safety in dengue-endemic countries. *Emerg Infect Dis;* **15**: 8-11 (2009).
11. Dhiman RC, Pahwa S, Dhillon GP, Dash AP. Climatechange and threat of vector-borne diseases in India:are we prepared? *Parasitol Res;* **106**: 763-73 (2010).
12. Myers RM, Carey DE. Concurrent Isolation frompatient of two arboviruses, Chikungunyaanddengue type 2. *Science*; **157**:1307-8 (1967).
13. Sudeep AB, Parashar D. Chikungunya: an overview.*Biosci;* **33**: 443-9 (2008).
14. Wang E Ni, H, Xu R, Barrett, AD, Watowich, SJ, Gubler, DJ, Weaver,SC. Evolutionary relationships of endemic/epidemic and sylvaticdengue viruses. *J Virol ;* **74**: 3227–3234 (2000).
15. Halstead SB. Dengue (Tropical Medicine: Science and Practice). River Edge, N.J: Imperial College Press. 2008. pp. 1–10
16. Dikid Indian J Med Res 138, July 2013, pp 19-31
17. NadkarJournal of the association of physicians of india• vol 62 • published on 1st of every month 1st september, 2014