

# EMERGING AND REMERGING VIRAL INFECTIONS IN INDIA

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**Abstract:** Viruses infect multiple hosts, including animal reservoirs, mutate rapidly and reassort or recombine, emerging and re-emerging to pose repeated threats to the human population. In recent years, India has successfully averted threats of human disease from emerging viral infections like SARS and avian influenza. However, through the last decade in India, viruses like Nipah and Chandipura viruses have led to outbreaks of viral encephalitis. Chikungunya has re-emerged with a vengeance, and the novel influenza A-H1N1 virus is spreading rapidly across the country. This review outlines the biology, epidemiology, clinical presentation and methods for the diagnosis of these viral infections, while also analyzing the reasons for their emergence or re-emergence and their potential future risk.

## INTRODUCTION

Infectious diseases are a major area of concern in human health and affect a large number of people worldwide. Despite the availability of various antimicrobials and vaccines, they remain the main cause of mortality. A majority of microbes, including viruses, exist in the immediate environment surrounding man, often maintained within other species, without causing human disease. However, due to various disturbances affecting the ecological balance, these microbes can, from time to time, emerge or re-emerge in human populations and cause sporadic disease or outbreaks. Some factors which help these agents to establish their pathogenicity include changes in human behavior, industrialisation, economic development, travel, geographical disasters and mass movement. Apart from this, global warming, deforestation, expanding urban slums, and changing social practices often lead to the emergence of these infections<sup>1</sup>.

Many of the diseases that have emerged or re-emerged in India in recent years are caused by viruses. High rates of mutation and antigenic change, along with rapid adaptation to newer ecosystems, makes them efficient at infecting new hosts including man, thus creating local or global health threats. This is especially true of viruses that contain ribonucleic acid (RNA), as these mutate rapidly during replication, and exhibit tremendous genetic plasticity due to the built-in advantages provided by their error-prone replicative enzymes and ability to genetically reassort (when their genome is segmented) or recombine<sup>1</sup>.

At the very onset, it is necessary to distinguish emerging or re-emerging viral infections from new viral infections, which are not included in this review. An example is the newly described human metapneumovirus (HMPV), also reported for the first time from India in recent years<sup>2</sup>, which is associated with acute respiratory tract infections, and belongs to the same family (*Paramyxoviridae*) as the respiratory syncytial virus (RSV) and the measles virus. Though HPMV was isolated only in 2001, antibodies to the virus were found to be present in sera collected as long back as 1958<sup>3</sup>. Unlike the avian and novel H1N1 influenza viruses, it has not crossed over recently from animal reservoirs to the human population. Therefore, this virus cannot be considered an emerging virus, unlike the new influenza viruses which have recently emerged as human pathogens. This review, which is focused only on India, also excludes emerging viruses for which no human cases have been reported from India, e.g. the coronavirus that caused severe acute respiratory syndrome (SARS) and the H5N1 avian influenza virus. We also decided to exclude dengue from this review, as it has been covered quite extensively elsewhere in recent years. Dengue, transmitted by the *Aedes* mosquito, re-emerged as a cause of viral haemorrhagic fever in the mid-1990s but should now be considered

an established disease, being hyper-endemic in many parts of India, with all four serotypes (1 to 4) of the dengue virus circulating simultaneously<sup>4</sup>, frequently causing outbreaks in some part or the other of India during the monsoon season, from time to time with haemorrhagic manifestations. Here, we focus on five emerging or re-emerging viral infections (Chikungunya, Hantaviruses, Nipah virus, Chandipura virus and the novel H1N1 influenza virus) that have attracted increased attention through the last decade in India, due to explosive or insidious debuts, alarming changes in disease spectrum or sudden spurts in numbers and geographical reach. We briefly outline their basic biology, epidemiology, clinical presentation, diagnosis, how they have emerged or re-emerged, as well as the current risk they represent.

## CHIKUNGUNYA

Chikungunya virus (CHIKV) infection, which has re-emerged in recent years, is caused by a single-stranded RNA virus belonging to the family *Togaviridae*, genus *Alphavirus*. It spreads by the bite of the *Aedes* mosquito. The sylvatic cycle between the mosquito and forest primates is found only in Africa. The virus was first isolated from Tanzania in 1953 and its name is derived from a Makonde word which means "that which bends up", in reference to the stooped posture as a result of the arthritic manifestations of the disease. Two different lineages of CHIKV are known, one from West Africa and the second from East/ Central/ South Africa, as well as Asia. The first outbreak in India occurred in 1963 in Kolkata, followed by another in Chennai in 1964. The virus continued to circulate until 1973, when there was a small outbreak in Maharashtra. Subsequently, over more than three decades, India was possibly free of this virus. However, widespread reports from Andhra Pradesh, announced its re-emergence in 2005<sup>5,6</sup>. This was preceded by outbreaks due to this East/ Central/ South African strain of CHIKV, in the islands of the south-western Indian Ocean, starting with the Reunion Islands. Since 2006, the virus has spread across many parts of India, causing a few million cases, especially in Karnataka, Maharashtra, Kerala and Tamil Nadu, with additional reports from Orissa, Madhya Pradesh, Rajasthan, Gujarat and Delhi<sup>5,6,7</sup>. Two reasons have been ascribed to this re-emergence. One is the build-up of a susceptible, non-immune population in India due to the absence of circulation of the virus. A study from Kolkata in the interim period showed a seroprevalence of only 4.4%, with the highest prevalence in the age-group<sup>5</sup>. The other reason is a unique mutation that emerged during the circulation of the current CHIKV strain, in the gene for the envelope protein E1, leading to a change in the amino acid at position 226 from alanine to valine (A226V). This has been associated with a higher epidemic potential and the possibility of transmission by *Aedes albopictus* in addition to *Aedes aegypti*, the traditional vector in India<sup>8</sup>.

The incubation period ranges from 1-12 days, but is usually 2- 3 days. The symptoms include fever of abrupt onset, with chills, headache, rash and myalgia, along with severe migratory polyarthralgia affecting various joints like those of the hands, wrists, ankles and feet. The fever lasts for 1- 7 days. The symptoms may be indistinguishable from dengue virus infection<sup>5</sup>, coinfection with which is also reported from India<sup>7</sup>. Patients infected with the current strain have also presented with non- classical manifestations including hemorrhages, lymph node enlargement, jaundice and meningoencephalitis<sup>5,6</sup>, some of which may be associated with the new mutations<sup>8</sup>.

The diagnostic tests during the viraemic phase (the first 2- 3 days of fever) include virus isolation in an *Aedes* mosquito- derived cell line or a reverse-transcription polymerase chain reaction (RT-PCR). CHIKV specific IgM antibodies, which appear around the fifth day and last for 1- 3 months, are most commonly detected by an IgM-capture enzyme linked immuno-sorbent assay (ELISA) or, in specialised virology laboratories, by the haemagglutination inhibition or neutralisation tests. In India, the CHIKV ELISA developed by the National Institute of Virology (NIV), Pune, is available in laboratories which are a part of the surveillance network of the National Vector-Borne Disease Control Programme (NVBDCP).

Chikungunya is a self limiting fever, though the arthralgia may persist for many months. No specific medication or vaccine is available. Rest and mild exercise may improve the acute joint symptoms. Control of the vector is the main mode for prevention of transmission.

## HANTAVIRUS

Hantaviruses are enveloped, single- stranded RNA viruses belonging to the family *Bunyaviridae*. They are most widely distributed as zoonotic rodent borne viruses. They cause a spectrum of clinical symptoms in humans ranging from sub clinical presentations to severe haemorrhagic fever with renal syndrome (HFRS) and pulmonary syndrome or cardiopulmonary syndrome (HCPS), where death is caused by cardiac failure rather than pulmonary edema. HFRS is common in Asia where as most of the cases of HCPS are seen in the Americas. Various hantavirus serotypes/ genotypes are pathogenic to human including those that are Hantaan virus (HTNV)- like, e.g. HTNV, Seoul virus (SEOV), Dobrava- Belgrade virus (DOBV), and Thailand virus (THAIV); Puumala virus (PUUV)- like; and Sin Nombre virus (SNV)- like hantaviruses. Hantaviruses have a tri-segmented genome, which codes for replicative enzymes, an envelope glycoprotein, and a nucleocapsid (N) protein. The latter is abundant and highly antigenic, eliciting a strong humoral response in early infection, thereby making it useful for diagnosis<sup>9</sup>.

The geographical distribution of hantaviruses closely reflects the distribution of their various rodent reservoirs, which exhibit asymptomatic and persistent infection despite the presence of serum neutralizing antibodies. Man can get infected through aerosols generated from virus-contaminated rodent urine and faeces, bites, scratches, and contaminated food. The incubation period ranges from 1- 5 weeks. The major manifestations vary depending on infecting serotype, as described earlier. However, early signs and symptoms are non-specific. The detection of virus specific IgM antibodies against the N antigen is the choice for early diagnosis. RT-PCR using genus specific and species specific primers can also be used for diagnosis in the acute stage.

The Thottapalayam virus (TPMV) was the first indigenous hantavirus species isolated from south India from a non-rodent insectivorous shrew, *Suncus murinus*, in 1964<sup>1</sup>. In 2000, human Hantavirus infection was confirmed for the first time in India from 9 cases of suspected leptospirosis, of which two cases (one from Kochi and

one from Chennai) developed dialysis-requiring acute renal failure with hypoxia which proved fatal<sup>10</sup>. The overall positivity in these suspected leptospirosis- like infections was 12% (17% in those with severe disease). Based on this rather low positivity for antibodies against PUUV (and, probably SEOV) hantaviruses, and the absence of any known rodent host in India (which is the norm for hantaviruses), the authors speculated that either there may exist a hitherto unknown Indian hantavirus or these cases could be due to the Thottapalayam virus itself. In 2005, Chandy et al<sup>11</sup> detected hantavirus- specific antibodies using both an IgM ELISA and an immunofluorescent assay (for antibodies to SEOV), in 18 (12%) of 152 patients with pyrexia. A small percentage of healthy blood donors were also positive for anti-hantavirus antibodies. By using truncated N protein derivatives of different Asian Hantaviruses for ELISA-based serotyping, Chandy et al (2009)<sup>12</sup> postulated that an unknown HNTV- like serotype could be circulating in India, in addition to the THAIV serotype. In 2007 it was reported that following floods in Mumbai in 2005, five of 11 cases admitted to the intensive care unit of a city hospital with fever (with or without haemorrhagic manifestations) were confirmed to have IgM antibodies to hantavirus, and one of these had ocular manifestations in the form of intraretinal haemorrhage<sup>13</sup>.

All these recent data suggest the presence of Hantavirus infections in India, even though questions may still remain about the particular serotype(s) that are prevalent. It is probable that hantaviruses are under-diagnosed in India due to a lack of awareness.

There is no definitive treatment available for Hantavirus infection. A few clinical trials with ribavirin in China showed a decrease in the fatality due to HFRS, but no marked improvement in HCPS. An inactivated vaccine is also licensed in Korea but the protective response is short-lived<sup>9</sup>.

## NIPAH VIRUS

Nipah virus (NiV) and Hendra virus (HeV) are closely related members of the family *Paramyxoviridae* and are included in a new genus, *Henipavirus*. HeV was first isolated in 1994 from an outbreak of respiratory and neurological disease in horses, and 3 humans infected by exposure to secretions from the infected horses, in Hendra, a suburb of Brisbane, Australia. Two of these cases died of a severe respiratory illness, while one developed delayed progressive encephalitis. HeV remains confined to Australia, where it caused two further outbreaks in 1995 and 1999.

Nipah virus was initially isolated in 1999 from an outbreak of encephalitis and respiratory illness among adult males who handled pigs in Malaysia in 1998-99. This was followed by an outbreak in Singapore. The virus also caused a relatively mild disease in pigs, which act as amplifier hosts. It was subsequently reported from different parts of world including Bangladesh (which had 8 outbreaks from 2001 through 2008), Australia, Thailand and Cambodia, causing severe fatal encephalitis<sup>14, 15</sup>.

*Pteropus* spp. fruit bats (flying foxes) are the natural reservoirs for both these viruses. They are distributed across the Indo-Pacific region. The virus is shed in the urine of bats and found in fruit partially eaten by them. Pigs get infected with Nipah virus by eating fruit contaminated with bat saliva or urine, drinking contaminated water, or by eating an aborted bat foetus. Pigs shed the virus in saliva, respiratory secretions and, probably, urine. Human cases and infections in domestic animals (dogs and cats) occur after close contact with pigs, through aerosols. Person to person transmission was documented in Bangladesh in 2004, and infection due to ingestion of contaminated raw date palm juice, has also been reported from Bangladesh<sup>14, 15, 16</sup>.

The first NiV outbreak in India occurred in January and February, 2001 in Siliguri, West Bengal and was reported in detail in 2006<sup>15</sup>. A total 66 cases of encephalitis were identified with a case fatality ratio of 74%. This rate was similar to the outbreaks in Bangladesh, in contrast to the earlier outbreaks in Malaysia and Singapore in which the case fatality ratio was much lower, at 40% and 9%, respectively. This suggests that the virus seen in Bangladesh and India is now more virulent. Though the index case was not identifiable, the outbreak started from one hospital and went on to involve 3 others. Most of the patients were either members of hospital staff or had attended to or visited patients in one of the four hospitals involved. Person to person transmission was seen. The virus is shed in respiratory secretions and urine.

The patients confirmed to be affected were all > 15 years of age, with males predominating (1.4:1)<sup>15</sup>. The incubation period ranged from 5 to 20 days, with a median duration of 10 days<sup>16</sup>. Clinically, fever and altered sensorium (confusion to coma) were present in nearly all the patients, while headache and myalgia, respiratory symptoms (tachypnea to acute respiratory distress), and involuntary movements or convulsions were present in approximately half the patients. A small number of patients had a history of vomiting. No neck rigidity or cranial nerve involvement was observed. In this outbreak, the aetiology was confirmed by an ELISA for NiV-specific antibodies and an RT-PCR from urine. Virus isolation was attempted from urine in the Vero E6 monkey kidney cell line, but was not successful<sup>15</sup>.

Due to the abundant presence of natural reservoir *Pteropus giganteus* in the north-eastern parts of India, and the demonstration of Nipah virus infection in these bats in regions of India as far removed as Haryana<sup>17</sup>, and another small outbreak in Nanded in West Bengal in 2007, it seems that future outbreaks are likely. Nevertheless, strengthening the surveillance system and implementation of various preventive measures, like the strict observation of standard (earlier, universal) precautions and the use of personal protective equipment in hospitals, would help control their spread.

## CHANDIPURA VIRUS

The Chandipura virus (CHP) belongs to the genus *Vesiculovirus*, family *Rhabdoviridae*. CHP is an enveloped RNA virus, transmitted by bite of the female sandfly (e.g. *Sergentomyia*). Though the virus has been isolated from Africa (Senegal and Nigeria) and Sri Lanka, and can infect many mammalian species, human cases are reported only from India<sup>18,19</sup>. CHP remained an orphan virus for a long period, unlinked to any particular illness because of its indistinct clinical features. It was first isolated in a case of fever from the Chandipura region (Nagpur), Maharashtra, in 1965<sup>20</sup>. Subsequently, it was isolated from a child with encephalitis in Raipur<sup>21</sup>. However, only after it was implicated as the cause of an epidemic of encephalitis-like illness in Andhra Pradesh in 2003 was it considered a potentially dangerous emerging virus<sup>22</sup>. The outbreak involved 329 children with symptoms resembling acute encephalitis. Subsequently, in 2004, the diagnosis of Chandipura virus was established in a similar outbreak in Gujarat<sup>23</sup>. These outbreaks strengthened its aetiological association with what has been variously reported as either an epidemic "brain attack" of childhood (EBAC) or Chandipura encephalitis<sup>18,19</sup> (when the diagnosis was supported by virus isolation, identification by electron microscopy, immunofluorescence and PCR).

All age groups are susceptible to this infection, with a higher incidence observed in children and young adults. The usual mild form of the illness is characterized by the sudden onset of fever with myalgia and arthralgia. However, the cases in Andhra Pradesh presented with

fever and altered sensorium, with no signs of meningeal involvement. The case fatality rate was 55% and death often occurred within 48 hours of onset. In the Gujarat outbreak, the male to female ratio was 1:1 and the ages of the patients ranged between 2 and 16 years (with a mean age of 6 years). The case-fatality rate was 78% with three-fourths of the deaths occurring within 24 hours of onset of disease, and the rest by 4 days post-onset. Neurological sequelae were not observed in survivors. The most common manifestations were fever, altered sensorium and convulsions, followed by vomiting and diarrhoea. Less common symptoms were chills, cough and vesicular eruptions. Deep tendon reflexes were lost in two-thirds of the patients, while a decrease in muscle tone and power, and bilateral lung crepitations, were detected in nearly half the patients. Hepatomegaly with disturbances in liver function, and hemiparesis with seventh cranial nerve palsy were rarer manifestations. The cerebrospinal fluid did not show any significant abnormality<sup>23</sup>.

During the Gujarat outbreak, CHP could be isolated from some cases in porcine stable (PS) and rhabdomyosarcoma (RD) cell lines. The virus was also grown in suckling Swiss albino mice inoculated intracerebrally. CHP-specific antibodies were demonstrated in only a few cases by an IgM ELISA and a neutralization test in cell culture, as most cases proved fatal before the antibodies could rise to detectable levels. RT-PCR for viral RNA in acute phase sera, which was found to be a most useful, sensitive and rapid diagnostic method, was positive in nearly half the cases. Though this technique could not detect CHP in sandflies collected from the affected areas in Gujarat, the virus had been isolated from sandflies during the outbreak in Andhra Pradesh<sup>23</sup>. Partial glycoprotein (G) gene sequencing revealed that the Gujarat isolates were homologous to the ones from the Andhra Pradesh outbreak, as well as to the virus isolated from Maharashtra in 1965<sup>23</sup>.

It needs to be mentioned that some controversies still remain regarding the role of this virus in paediatric illnesses. There is a high prevalence of specific antibodies and viral RNA in apparently healthy populations in India<sup>23</sup>. Further, though there is histopathological evidence of an inflammatory reaction in the brains of mice, this is not seen in humans. This had also led to the diagnosis of encephalitis being challenged earlier and it has been suggested that CHP may just be a passenger virus or a concomitant virus in humans<sup>18,19</sup>. Further outbreaks should provide an opportunity to resolve these issues.

## NOVEL H1N1 INFLUENZA VIRUS

Influenza has drawn worldwide attention for being one of most common infectious agent causing significant morbidity and mortality. The influenza virus is an enveloped RNA virus with eight segmented genome belonging to the family *Orthomyxoviridae*. The envelope has two sets of protruding protein spikes, the haemagglutinin (HA) and the neuraminidase (NA). The influenza virus has three types, A, B, and C. Influenza A virus has 16 HA and 9 NA subtypes. It has a wide range of host including birds, pigs, horses, sea mammals, and humans. Aquatic birds are the natural reservoir allowing replication and mutation of the virus. Human gets infection through birds and pigs mainly. Hence, these two species are known as "melting pots", playing a major role in the global spread of influenza virus. Because of the possibility of reassortment of genome segments between influenza viruses from human hosts and other species (leading to an antigenic shift), as well as the high rate of point mutation (leading to an antigenic drift), a high rate of genetic diversity is observed.

The first pandemic by the influenza A virus (H1N1) occurred in 1918. It is popularly known as "Spanish flu" causing the death of nearly 40 million people worldwide. Subsequently, the "Asian flu" (H2N2) and "Hong Kong flu" (H3N2) occurred in 1957 and 1968,

respectively. Until recently, H3N2 and (classical) H1N1 remained the major virus subtypes causing disease (seasonal influenza) in humans. In 1997, the H5N1 strain of avian influenza emerged in poultry, with a few closely-associated human cases, in central Asia. This virus soon mutated to a highly pathogenic avian influenza (HPAI) virus, causing 100% mortality in chickens within 48 hours, which first spread in poultry across the Asia Pacific, and then to other continents. This spread in poultry, through the faeco-oral route, was accompanied by human cases with a high case fatality rate in those infected through direct contact, by inhalation of aerosolized bird droppings. However, no large scale human-to-human transmission was recorded. The first confirmed case of avian influenza from India was reported on 18 February 2006 from a poultry farm in the Nandurbar district of Maharashtra. It spread to adjoining parts of Maharashtra, Madhya Pradesh and Gujarat. Rapid destruction of poultry by culling of infected birds, proper disposal of carcasses and quarantining prevented any human infection during this outbreak in poultry, as well as subsequent ones in Manipur and West Bengal.

In April 2009, an outbreak due to another influenza virus, originally believed to be only of swine origin, was recognized between the borders of Mexico and United States. This was caused by the novel H1N1 virus (which is different from the 1918 "Spanish flu" virus). On subsequent analysis, the novel H1N1 virus was found to be a triple reassortant carrying gene segments from swine (multiple strains), avian and human influenza viruses. These included haemagglutinin (HA), nucleocapsid protein (NP), and nonstructural protein gene segments from a swine influenza A virus, polymerase genes (PB2, PA) gene segments from an avian influenza virus, and the polymerase (PB1) gene segment from a human influenza A virus. The neuraminidase (NA) and matrix protein (M) segments were derived from another swine influenza virus of Eurasian origin<sup>24</sup>.

As of 20 December 2009, worldwide more than 208 countries and overseas territories or communities have reported laboratory confirmed cases of the novel pandemic influenza H1N1 including at least 11516 deaths. The United States, Mexico, and Canada have accounted for more than 80% of the total number of cases worldwide. Influenza activity was continuing to increase in the northern India<sup>25</sup>. The first "imported" case of novel H1N1 influenza in India was detected on 13 May 2009 from Hyderabad airport. Subsequently, the pandemic spread rapidly throughout India, with more and more cases being confirmed by the recommended real-time PCR and reported from across the country. By 23 December 2009, 24439 cases had been reported with 811 deaths, according to the official data release of the Government of India<sup>26</sup>.

The clinical features of this ongoing outbreak include a self-limiting febrile illness and respiratory symptoms (like cough and nasal discharge), which is similar to seasonal influenza due to the previously prevalent H3N2 and H1N1. However, about a third of the cases it may be associated with diarrhea or vomiting. Patients from high-risk groups may progress to pneumonia and acute respiratory distress. The first death due to swine flu was first reported from Pune in August, and was followed by other reports of mortality. However, it must be noted that the risk of pandemic H1N1 influenza is rated as moderate by the World Health Organisation (WHO), with those at the extremes of age and with underlying pulmonary and other high-risk conditions more likely to suffer serious illness. However, compared with seasonal influenza, the H1N1 virus affects a much younger age group in all categories – those most frequently infected, hospitalized, requiring intensive care, and dying<sup>25</sup>.

Samples from the upper respiratory tract (a throat swab, nasal swab or nasopharyngeal aspirate) can be collected and tested by the real-

time PCR (or culture), which are the recommended procedures for the laboratory diagnosis of novel H1N1, and are available through laboratories associated with the influenza surveillance network and approved private laboratories. The available commercial rapid tests detect seasonal influenza but are not recommended to be used to test for the novel H1N1 virus.

Patients with mild illness are observed and provided supportive care. Laboratory-confirmed cases and critically ill patients suspected to have swine flu should be administered antivirals. The novel H1N1 is susceptible to neuraminidase inhibitors i.e. oseltamivir and zanamivir. A pandemic vaccine has already been developed and is now being deployed by the WHO.

A comprehensive plan, which includes active surveillance, strengthening of research, and promotion of the development of indigenous vaccines and local production of antiviral drugs, is already being implemented and should, in the near future, help to minimize the damage being caused by this pandemic in India.

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