Scholars Academic Journal of Pharmacy
Abbreviated Key Title: Sch Acad J Pharm
ISSN 2347-9531 (Print) | ISSN 2320-4206 (Online)
Journal homepage: http://saspublishers.com

OPEN ACCESS

Pharmacy Practice

Major Viral Outbreaks in the 1st Decade of 21st Century- Literature Review

Dr. Nithish Sattoju[1*], Pranay Reddy R[2], Vinay Surisetty[2]

[1]Assistant Professor, Department of Pharmacy Practice, Chilkur Balaji College of Pharmacy, Hyderabad, Telangana, India
[2]Pharm. D, Chilkur Balaji College of Pharmacy, Hyderabad, Telangana, India

DOI: 10.36347/sajp.2023.v12i10.002 | **Received:** 07.09.2023 | **Accepted:** 12.10.2023 | **Published:** 20.10.2023

***Corresponding author:** Dr. Nithish Sattoju
Assistant Professor, Department of Pharmacy Practice, Chilkur Balaji College of Pharmacy, Hyderabad, Telangana, India

Abstract **Review Article**

21st century has experienced several viral outbreaks, top of which is the severe acute respiratory syndrome- Corona Virus -2 (SARS- CoV-2/ COVID-19) that crossed all the borders and invaded human kind and health care settings with erupting mortality rate as never seen before and reshaping the global health care perspectives and responses. Besides COVID-19, there are several viral outbreaks seen in different countries which were confined to its region and were declared as the epidemic or endemic due to its widespread infection. The current review focuses 5 such viral outbreaks that were declared epidemic or endemic and resulted in disruption of health care system of that nation and highlights on its pathophysiology and our position in its treatment and vaccination status. The review included viral outbreaks of measles, avian flu, hendra, crimean-congo hemorrhagic fever, swan flu. Choice of these viral outbreaks was made after through search for all the potent outbreaks in the 1st decade of 21st century i.e., from 2000 to 2010, as per World Health Organisation (WHO) reports and factsheets. We abide with the fact that many other outbreaks were missed in this review. However, efforts were made to detail the selected outbreaks. Most of the viral outbreaks were seen with more than one outbreak and one nation which are detailed along with its familial hierarchy. Most comprehensive research was carried out to ensure no detail on its available treatment and vaccines were missed.

Keywords: Viral Outbreaks, Epidemic, Endemic, Vaccination, Treatment.

INTRODUCTION

1. MEASLES

Measles is a highly contagious airborne disease that spreads easily from one person to another and is caused by measles virus (single stranded, negative sense, enveloped RNA virus) of Morbillivirus genus and Paramyxoviridae family [1]. Measles is also called Rubeola [2]. The symptoms usually develop 10 – 12 days after exposure to an infected person which lasts for about 7 – 10 days [2].

Measles is a highly contagious virus that resides in the nasal and throat mucous of an infected person. It can spread through coughing or sneezing. If people breathe in contaminated air or touch infected surface and touch their eyes, nose or mouth, they become infected. If a person comes in contact with infected person, they can get infected. The spread ratio is about 90%, which mean if one person has the infection, up to 9 out of 10 people can be affected. Infected people can spread measles to others from four days before and after the rash appears. Virus can live up to two hours in air after infected person leaves an area [3].

Measles is found to be as far back as the 7th century A.D. In 1757, the demonstration of measles caused by infectious agent in blood of a patient was known. In 1954, the virus causing measles was isolated in Boston, Massachusetts by John. F. Enders and Thomas C Peebles. In 9th century, a Persian doctor first published written account of measles disease [4, 5].

The known hosts of measles are humans alone. More than 90% of children were affected by measles below 15 years of age before vaccine introduction. But after the introduction of vaccine, the disease has been in good control mostly in the developed countries. Globally, the number of reported cases has gone down from 146 cases per million in 2000 to 36 cases per million in 2015. In the year 2015, Africa has reported the highest number of cases followed by Western Pacific and South- East Asia. If we look into the current situation, the cases of measles in developed countries are the

"imported" cases from endemic countries and of vaccinated or partially vaccinated individuals. The outbreaks in the developed countries can be due to refused or negligence of vaccine.

The characterisation of measles virus has helped in identification of 8 classes of measles virus i.e., from A – H and further subdivided into 24 genotypes. The classified group of viruses circulates in different regions all over the world. Group A mainly circulates in the U.S, Russia, Argentina, China and the U.K. Group B and C are seen in South Africa, Philippines, and Japan. Group D and E are seen mainly in Western Europe. Group F in Africa. Group G in Indonesia, Canada, and Malaysia. Japan, China, and Korea are regions mostly with Group H circulation [6].

In the 1920's, the death rate or fatality rate was approximately 30% of all infected persons. But it has decreased to less than 0.5% because of the healthcare systems and improved hospitalisation. Mortality is about 10% in the individuals with high malnutrition levels. It can go up to 20-30% in case of serious complications. There has been a drop of 65%-75% in case of deaths because of immunisation. Globally, measles fell significantly from an estimated 873,000 in 1999 to 345,000 in 2005 and approximately 57,000 in 2014 [7]. Measles has been spread throughout the world. Initially there were many cases reported but as time passed on and because of improved hospitalisation, healthcare systems and vaccination, the number of cases reported and deaths has decreased. Globally, the most cases reported are from the African region followed by Western Pacific region and European region. The table 1 below presents the measles cases reported according to WHO statistics [7].

Table 1: Number of measles cases reported in various regions as per WHO statistics

Region	**1980**	**1990**	**2000**	**2005**	**2014**
African region	1240993	481204	520102	316224	12125
Western Pacific	1319640	155490	176493	128016	34310
European region	851849	234827	37421	37332	2430
South-East Asia	199535	224925	61975	83627	1540
Region of the Americas	257790	218579	1755	19	3100
Eastern Mediterranean	341624	59058	38592	15069	2214
Worldwide	4211431	1374083	836338	580287	55719

In measles, both sexes are equally affected. The most susceptible age group is of young children. When compared, the infants born to mothers with vaccine-induced immunity are more susceptible to measles at earlier age than those born to natural acquired immune mothers. The other risk factors include infants who are very young to be vaccinated, travelling to endemic areas, partial or no vaccination, Vitamin A deficiency, malnutrition etc. Measles is most common in late winter and early spring in temperate climates [6].

The signs and symptoms appear around 10-14 days after exposure to virus. The typical ones include fever, dry cough, runny nose, skin rashes, inflammation of eyes (conjunctivitis), tiny white spots with bluish-white centers on red background found inside on the inner lining of mouth (Koplik's spots) around 2-3 days of infection. Fever is usually more than 40°C (104°F). After 3-5 days, red flat rashes start on face and spreads to rest of the body [2].

There are different stages during infection within a period of 2-3 weeks. During the infection and incubation period there will be no symptoms seen. But few non-specific signs and symptoms are observed which includes mild to moderate fever, cough, runny nose, conjunctivitis, sore throat etc. which can stay up to 2-3 days. Later small red spots appear, these spots bumps in tight clusters with red appearance of the skin. Rashes from face continue to arms and trunk, lower legs, feet etc. and high fever is observed. The communicable period is approximately 8 days which means 4 days before and 4 days after rash appears. Some common complications include diarrhoea, pneumonia, middle ear infection [2].

Measles is a highly contagious virus and when a person comes in contact to the contaminated air or an infected person directly, they can easily get infected [3]. When the droplets with virus are exposed in the air and are inhaled, the virus enters into the body in one or the other ways. The lymphocytes of respiratory tract are infected initially with dendritic cells and macrophages. Then it spread to the lymphoid tissues thereon enters the bloodstream which leads to presence of virus in the blood (viremia) and reach the distant organs. The virus is transferred to epithelial cells of lungs from dendritic cells and lymphocytes of lungs where it previously resided. These are then shed and expelled as respiratory droplets when a person involves in coughing and sneezing. So, when the virus is expelled out, it creates a chance of spreading and causing infection in others, which cycle continues. The virus also causes inflammation which are then known by symptoms like coryza, cough, conjunctivitis etc. After the virus entered the bloodstream pyrexia is seen. Skin rashes are observed after complete spread or dissemination of virus and seen because of perivascular and lymphocytic infiltrates. In the period between appearance of initial symptoms and full development of rash and fever, the virus depresses host immunity. This is done by decreasing the interferon production. There is an increase in the rates of viral replication which activate cellular and humoral

immunological responses. Then there is production of IgM and IgG antibodies during the initial humoral response of which the former is observable for 3-4 days after rash appearance and can continue for 6-8 weeks [8].

The increase in levels of Th1 dependent plasma interferon-gamma, Th2 dependent IL-4, IL-10, IL-13 demonstrates the cellular immune response. As the measles virus cause immunosuppression, there are more chances for the host to develop secondary bacterial and other infections which can continue for weeks to months or even years. The exact mechanism for immunosuppression is unknown but as per hypothesis it is because of the proliferation of measles-specific lymphocytes which replace memory cells already established. This is called "Immune amnesia". Because of this very reason, the host's immune system is suppressed and affected by other complications and mortality. The neutralising IgG antibodies are responsible for lifelong immunity as they block cell receptors from binding to cells [8].

There is no specific treatment for measles except supportive care to relieve symptoms associated with the condition. Various measures like antipyretics for fever, hydration, nutritional support is necessary. There is also no specific availability of antivirals to treat measles. It mainly consists of nutritional therapy, prevent dehydration and also to detect and treat secondary bacterial infections. According to studies, it has been understood that children with measles tend to have low serum levels of retinol and it decreases more with disease progression. So, administration of high doses of Vitamin A have been shown to decrease death rate and also the risk of complications in patients hospitalised with measles [9, 10].

Vitamin A plays a major role in maintenance of epithelial tissue and immunological function. In infectious condition, levels of Vitamin A decreases resulting in its deficiency and making the person prone for secondary infections. Antibiotics should be administered in case of bacterial infections like pneumonia, sepsis etc. If the patients are exposed to measles or show no evidence of immunity, then it can be treated by various ways. In case of pediatric patients & for infants of 0-5 months of age, immunoglobulin administration is recommended within 6 days of exposure. If the infant is of age 6-11 months, measles vaccination within 72 hours or immunoglobulin within 6 days of exposure is recommended. For children of age more than 12 months, vaccination is preferred over immunoglobulin administration within 72 hours, or along with immunoglobulin. In case of pregnancy, it is recommended for administration of immunoglobulin and vaccine is contraindicated. If a patient is immunocompromised then immunoglobulin is preferred irrespective of vaccination status. Immunoglobulin administration is recommended critically for patients at high risk of complications like pregnancy, infants and immunocompromised status [9, 10].

As per advisory committee on Immunisation practices, a dose of 0.5 ml per kg of body weight is administered intramuscularly for people with body weight up to 30kg and 400 mg per kg through intravenous route if body weight more than 30 kg. The immunity by immunoglobulin administration is for a short period of time. So, this should usually be followed by receiving MMR vaccine with minimum gap of 6-8 months after immunoglobulin administration. For immunocompromised patients, immunoglobulin administration has to be continued even after vaccination, as they might not be protected by vaccination. The doses of Vitamin A administered differs for various age groups. For infants less than 6 months of age 50,000 IU is recommended. For children of age 6-12 months and children above 12 months, 1,00,000 IU and 2,00,000 IU respectively are the recommended doses of Vitamin A [9, 10].

American Biomedical scientist John. F. Enders and Dr. Thomas C Peebles who was an American physician collected samples of ill patients during a measles outbreak in Boston, Massachusetts in the year 1954. The prime aim was the isolation of measles virus to develop a vaccine against measles, which they were successfully able to isolate from a 13year old patient David Edmonston's blood. In the year 1963, John. F. Enders and colleagues have developed a vaccine by transformation of Edmonston-B strain of measles and licensed it in the U.S. Following this, an even more weaker and improved measles vaccine was developed by Maurice Hilleman and colleagues in 1968 and begun to distribute. From there on, this vaccine which is called the Edmonston-Enders strain has been the only measles vaccine being used, formerly known as 'Moraten'. The measles vaccine is usually combined with mumps and rubella (MMR) or with mumps, rubella and varicella (MMRV) [5].

Measles therefore can be prevented by the use of MMR vaccine. The MMR vaccine protects against three diseases, namely measles, mumps, and rubella. It is recommended that two doses of MMR vaccine are to be taken. The first dose at 12 – 15 months of age and the second dose at 4 – 6 years of age. Teens and adults should also be up to date about their MMR vaccination. This vaccine is very safe and effective. It provides about 97% effectiveness for two doses and around 93% effectiveness for one dose of MMR vaccine [11].

MMRV vaccine is another vaccine that can be used. It protects against four diseases which include measles, mumps, rubella, and varicella. This is usually used for children who are above 12 months & up to 12 years of age [11]. The table 2 presented below lists the MMR vaccines with brand names and its availability in different countries [12, 13].

Table 2: MMR vaccines brand names and availability in different nations

Brand name	Country Availability
M-M-R II	The U.S, Thailand, Australia, Canada, Czech Republic, Indonesia, Malaysia, New Zealand.
M-M-R Vax	Austria, Germany.
M-M-R Vaxpro	Iceland, Lithuania, Slovenia, Slovak republic.
MMR	Vietnam, UAE, Taiwan, Switzerland, Argentina, Bahrain, China, Egypt, Great Britain, Hong Kong, South Korea, Liechtenstein, Philippines, Norway, Saudi Arabia, Qatar, Sweden
Pluserix	Burkina Faso, Benin, Bermuda, Bahamas, Belize, Cote D'Ivoire, Ethiopia, Ghana, Gambia, Guyana, Liberia, Morocco, Mali, Mauritania, Malawi, Niger, Nigeria, Netherlands, Seychelles, Sudan, Sierra Leone, Suriname, Tunisia, Trinidad and Tobago, Tanzania, South Africa, Zambia, Zimbabwe, Barbados, Guinea, Uganda, Mauritius, Jamaica, Kenya, Senegal.
Priorix	Australia, Barbados, Bahamas, Belize, Canada, Cyprus, Guyana, Ireland, Israel, Jamaica, Kuwait, Lebanon, Liechtenstein, Netherlands, Norway, Saudi Arabia, Spain, Suriname, Sweden, Trinidad and Tobago, Taiwan, United Arab Emirates, South Korea, Bermuda, Great Britain, Philippines, Sri Lanka, Romania, India.
Mumeru Vax	Philippines
ROR Vax	France
Prioryks	United Arab Emirates
Triviraten Berna	Malaysia, Thailand, Philippines, Hong Kong, New Zealand
Trimovax	Hong Kong, Pakistan, Taiwan, United Arab Emirates, Bulgaria, Thailand, Italy, India.

2. AVIAN INFLUENZA (AVIAN FLU)

Avian Influenza is the disease caused by Bird Influenza (avian flu) Type A belonging to Influenza A genus of Orthomyxoviridae family [14]. Various animals like ducks, chicken, pigs, horses, etc are being affected by Influenza A viruses. Transmission of virus from animals to humans is seen. H3N2 and H1N1 viruses are the Influenza A subtypes in Humans which are currently circulating [15].

Avian flu virus does not usually infect humans but few sporadic infections have been reported [16]. There are various subtypes like A(H5N1), A(H7N9) which cause serious infections. Other subtypes like H7N3, H7N7, H9N2, H5N6 also cause infections in humans. The infections in humans usually occur when the person comes into contact with infected birds or influenza contaminated surfaces in an unprotected manner, viz, when virus gets into the person's eyes, mouth, nose, etc or inhaled in some or the other way. This can happen when the person touches the virus contaminated surfaces and makes contact with his/her eyes, mouth, nose, etc. In other case, it can be easily inhaled when virus is in droplet/dust form. The resulting infection could be in a range of mild to severe infection [14, 17].

The first detected case of Avian influenza A(H5N1) in humans was in 1997 in Hong Kong, China, where it infected both chickens as well as people. This was the first time the humans were directly infected and around18 people were hospitalised of which 6 people were dead. To bring the situation under control, about 1.5 million chickens were killed [18].

Re-emergence of H5N1 was seen in 2003 from poultry in Asia, Europe & Africa. Around 17 countries have reported 862 laboratory confirmed cases of A(H5N1) virus. This includes 455 deaths since 2003 till the year 2021. Out of the 17 countries, 4 are from Southeast Asia region, viz, Bangladesh, Myanmar, Indonesia, and Thailand [14, 19, 20].

There have been 10 laboratory confirmed cases of Avian Influenza A(H5N6) in China since 2013 of which all 10 resulted in deaths [14]. Avian Influenza A(H7N9) subtype was first detected in March 2013 in China. A total of over 1500 laboratory confirmed cases of this virus were reported since then as confirmed by WHO(21). There have been 28 laboratory confirmed cases of Avian Influenza A(H9N2) virus globally [14].

Total of 17 nations reported cases of Avian Flu. The cumulative number of confirmed human cases for Avian Influenza A(H5N1) were reported to WHO. The table 3 below provides country wise information about no. of cases & deaths by A(H5N1) subtype reported to W.H.O. since 2003 [19, 20].

Table 3: Number of cases and deaths by H5N1 virus in different countries from 2003 to 2021 as per WHO statistics

Name of the country	H5N1 Cases from the year 2003-2021	
	Cases (in millions)	Deaths (in millions)
Egypt	359	120
Indonesia	200	168
Vietnam	127	64
Cambodia	56	37

Name of the country	H5N1 Cases from the year 2003-2021	
	Cases (in millions)	Deaths (in millions)
China	53	31
Thailand	25	17
Turkey	12	4
Azerbaijan	8	5
Bangladesh	8	1
Iraq	3	2
Laos	3	2
Pakistan	3	1
Canada	1	1
Nepal	1	1
Nigeria	1	1
Djibouti	1	0
Myanmar	1	0
Total	**862**	**455**

There is a high mortality rate of Avian Influenza i.e., > 60% for H5N1 and 30% for H7N9 approximately. Avian Influenza has high case – fatality rate among persons aged 10-39 years. Out of all the reported cases, half of the cases are in people below the age of 20 years of age and with 40% of cases involve the age group of 20 – 40 years [22].

Humans infected with avian flu may present fever, cough, sore throat, muscle aches, body pain, eye infections, pneumonia, acute respiratory distress & viral pneumonia. There can also be other severe and life-threatening complications too [18].

The main symptoms may range from mild upper respiratory infection (fever and cough) which can rapidly progress to severe pneumonia, acute respiratory distress syndrome, shock and death in some cases too. Various Gastrointestinal symptoms like nausea, vomiting, diarrhoea, are reported in Avian influenza A(H5N1) infection. Mostly the initial symptoms in A(H5N1) and A(H7N9) infections include high fever (≥ 38^0C), cough, dyspnea, breathing difficulty. Sore throat or coryza are less observed comparatively. Other symptoms like diarrhoea, abdominal pain, vomiting, nose and gum bleeding, encephalitis were also reported. This may lead to severe pneumonia, multi organ dysfunction, respiratory failure due to hypoxemia, septic shock and other bacterial, fungal infections [21].

The incubation period for A(H5N1) virus is 2-5 days and may range up to 17 days. For A(H7N9) virus it is 1-10 days with an average of 5 days [21].

The pathophysiology of H5N1 influenza involves various factors and tissue damage and disease outcome on the factors involved in dysregulation of cytokines and chemokines along with viral replication causing injury. Other factors include decreased CD8+ lymphocytes cytotoxicity and increased cell response of Tumour necrosis factor Related Apoptosis Inducing Ligand (TRAIL), whose roles are not clearly known [23].

Viral Replication – In general, viral replication of H5N1 causes cell and organ damage by apoptotic or cytolytic mechanisms. The virus replicates in the respiratory tract & seems to be for longer duration in case of H5N1 subtype because when plotted against time, viral loads did not show a decline clearly in most of the patients. In pharyngeal and nasal specimens' viral RNA levels were found higher. Through RT-PCR and in-situ hybridisation, viral replication in trachea and lungs is proven. Ex-vivo experiments provided evidence for the infection of nasopharynx and lungs with H5N1. Alongside, the intestines, brain, heart and placenta have been found with positive stranded RNA [23].

Dysregulation of cytokines and chemokines- The increased production of pro inflammatory cytokines and chemokines is found to play a crucial role in H5N1 infection. The above-mentioned process i.e., the viral replication process in turn leads to haemophagocytic activity. Elevated serum levels of pro inflammatory cytokines, TNF-α and chemokines is observed. The lungs of H5N1 infected case shows increased production of macrophages, inflammatory Protein - 1α, regulated on activation normal T-cell expressed and secreted (RANTES), Interferon- α, Interferon- β & IL-6. There is induction of greater production of chemokines and cytokines in human macrophages and respiratory epithelial cells [23].

Up-regulation of TRAIL and Apoptosis, Reduced cytotoxicity of CD8+ lymphocytes- There is higher expression of TNF-α and TRAIL in macrophages infected with H5N1 virus in-vitro than in other influenza viruses. Also, T- lymphocytes co-cultured with macrophages infected with H5N1 virus exhibit increased apoptosis. This in turn leads to increased sensitisation of virus infected T-lymphocytes to death receptor ligand-induced apoptosis. Lymphopenia and lung injury are commonly observed because of up-regulation of TRAIL. If the macrophages stay for longer periods, they increase the chances of apoptosis in T-lymphocytes. The cytokines and chemokines are produced and released for

prolonged periods by macrophages. The apoptosis occurs majorly in leukocytes of lungs, alveolar epithelial cells, intestinal tissues and spleen. Direct Viral replication and up-regulation of chemokines and cytokines leads to apoptosis. In case of H5N1 viruses, the perforin is suppressed in cytotoxic T-lymphocytes. The suppression may lead to impairment in cytotoxic activity which causes failure in clearance of H5N1 virus protein bearing cells and antigen presenting cells. The stimulation of cytotoxic T-lymphocytes cause production of Interferon-γ. This again leads to up-regulation of cytokines in macrophages [23].

The Influenza viruses are differentiated on the basis of antigenicity of their two surface glycol proteins, namely HA (Haemagglutinin) and NA (Neuraminidase). There are 16 HA's and 9 NA's found till now. Influenza A genome consists of eight gene segments encoding 11 proteins which include HA, NA, Polymerase proteins (PB1, PB2, PA, PB1-F2), NP (NS1, NS2), M1 and M2 [23].

Oseltamivir is an antiviral agent usually available in the form of oral formulations & is primary choice in treatment for A(H5N1) virus infection. As for now, there is no controlled clinical trials data available for Oseltamivir or other antivirals for A(H5N1) virus infection treatment. As per some observational studies, it has been understood that Oseltamivir can reduce mortality in these patients. Usually, a 5-day standard treatment is been advised until complications seen. The optimal regimen for treatment with Oseltamivir is still not properly known in Avian Influenza as it is much complicated than seasonal influenza. So, the standard dose and duration of Oseltamivir is known from studies of uncomplicated seasonal influenza. But due to lack of clinical trial data, the standard regimen in case of A(H5N1) virus infection cannot be exactly known. Therefore, the dose and duration of antiviral therapy should be guided by clinical course of disease in patient. If in case there is no improvement seen after the initial 5-day course, it has to be extended for another 5 days [24].

Neuraminidase Inhibitors (Zanamivir and Peramivir) are also used in the treatment of A(H5N1) virus infection. In most cases reported and treated, Oseltamivir has been the most used antiviral agent for treatment of the infection. There is limited information about the usage of other antivirals in the treatment of A(H5N1) influenza. Use of Zanamivir (inhaled) has not been studied in humans A(H5N1) illness but are actually active in-vitro and also in animal models, including the Oseltamivir resistant A(H5N1) virus infection. The parenterally administered Neuraminidase Inhibitors which are in clinical development (Zanamivir and Peramivir) give reliable drug delivery and also increased systemic drug levels. They have shown or given some desired actions in animal models and also in Oseltamivir-resistant variants. So, based on these studies, parenteral Zanamivir or Peramivir can be used as an alternative to oral Oseltamivir in the initial treatment of human A(H5N1) infection upon approval by National Regulatory Authorities [24].

Adamantanes (Amantadine and Rimantadine) have shown clinical benefits in patients with adamantine-susceptible A(H5N1) virus infection. But, when seasonal influenza was treated only with this drug, it has shown high frequency of rapid resistance and even the other viruses like A(H3N2) and A(H1N1) have shown resistance to Adamantanes [24].

Combination therapy is also an option of treatment. When Adamantanes and Oseltamivir were used as combination in preclinical studies, increased antiviral action and also decreased emergence of resistant viruses are seen. The same combination when studied in a mouse model infected with amantadine-susceptible A(H5N1) virus, it resulted in increased survival and antiviral activity compared to monotherapy, excluding in adamantane- resistant virus [24].

Patients who are hospitalised with A(H5N1) virus infection mostly have pneumonia as well. With simultaneously diagnosing, antibiotics can be given. The patients admitted in ICU are usually treated with combination of β – lactam (Cefotaxime, Ceftriaxone, or Ampicillin-Sulbactam) and Azithromycin / Fluoroquinolone. If laboratory tests give evidence or confirm A(H5N1) virus infection and no bacteriological cause of Community Acquired Pneumonia (CAP) then empirical antibiotic treatment has to be ceased. It has to be stopped, because use of antibiotics in A(H5N1) virus infections is not warranted as it is of no proven benefit and in addition cause side effects and develop bacterial resistance [24].

Corticosteroids have been used in treatment of Acute Lung Disease (ALD) / Acute Respiratory Distress Syndrome (ARDS) which is because of A(H5N1) disease. They have been used as they provide anti-fibrotic and anti-inflammatory effects. But there is no proper clinical advantage observed. In short, the corticosteroids are not widely recommended in the case of A(H5N1) virus infection. There is no clear benefit in treatment of A(H5N1) virus- associated pneumonia or ARDS with corticosteroids, in turn it can cause harmful effects like immune suppression, viral replication, secondary infections or side effects relating to Musculo-skeleton. But these can be used in low doses to treat refractory septic shock [24].

Two inactivated Avian influenza vaccines, including adjuvanted and unadjuvanted influenza A(H5N1) vaccines are licensed in The United States [25].

Table 4: H5N1 vaccines with its approval status

Name	Manufacturer	Approved for
Influenza A(H5N1) virus monovalent vaccine, adjuvanted [27].	ID Biomedical Corporation of Quebec	Use in persons of age six months or older at increased risk of exposure to Influenza A virus H5N1 subtype contained in the vaccine [26].
Influenza A(H5N1) virus monovalent vaccine, adjuvanted [27]. Trade name – AUDENZ	Seqirus, Inc.	Use in persons of age six months and above at increased risk of exposure to Influenza A virus H5N1 subtype contained in the vaccine [27].

Table 5: H5N1 Vaccines currently in clinical trial

Sponsor	Study type & phase	Intervention
Novartis Vaccines	Interventional, Phase –II	Biological: H5N1 influenza vaccine with 7.5 micrograms of H5N1 influenza antigen. Biological: H5N1 influenza vaccine with 15.0 micrograms of H5N1 influenza antigen [28].
National Institute of Allergy and Infectious Diseases (NIAID)	Interventional, Phase – I	Biological: Influenza virus vaccine, Live attenuated H7N9 Anhui 2013/AA ca. Biological: Monovalent A/H7N9 A/Shanghai/2/2013. Drug: MF59 adjuvant [28].
Institute of Vaccines and Medical Biologicals, Vietnam.	Interventional, Phase – II & Phase – III.	Biological: IVACFLU-A/H5N1 vaccine Biological: Placebo [28].
Novartis Vaccines	Interventional, Phase – II	With MF59-adjuvanted or non-adjuvanted H5N3 influenza vaccines [28].

3. HENDRA VIRUS

Hendra virus (HeV) is a rare emerging zoonosis that causes severe and often fatal diseases in both infected horses and humans [29]. Hendra virus belongs to the family- Mononegavirales, subfamily – Paramyxoviridae, genus – Henipavirus, species – Hendra virus. The natural host of the virus has been identified as a fruit bat and flying fox belonging to the family Pteropodidae and genus- Pteropus [30].

Virions are enveloped with a non-segmented, SS, negative sense ribonucleic acid genome that is 18,234 nucleotides in length. HeV is covered with two kinds of spikes that are 10nm & 18nm long which gives a double fringed appearance. These spikes contain F(fusion) glycoprotein trimers and G (attachment) glycoprotein trimers. Hendra & Nipah virus share 68 - 92% amino acid identity in their protein-coding and 40-60% of nucleotide homology [31].

1st case of the virus was recorded in Hendra, a suburb of Brisbane, Australia, in September 1994 [29]. Serological evidence of HeV infection has been found in all four species of Australian flying foxes. Viral RNA has been detected in urine of flying foxes of species Pteropus Alecto and Pteropus conspicillatus, vertical transmission and recurrence of infection has been reported in flying foxes but horizontal transmission is widely the primary mode of transmission. People living within the distribution of flying foxes and with occupational exposure to horses are at higher risk of HeV infection. It is not certain that how a virus could transmit from flying foxes to horses, it could be transmitted through equine contact i.e by oro-nasal, conjunctival fluids or by urine of infected flying fox directly or by these fluids contaminated pasture or the surfaces [30, 32]. Transmission of the virus from animals to humans could be through physical contact with nasal and oral secretions emanating from ill or dead horses [30]. But transmission of virus from flying fox to human cases has not been recorded [32].

Table 6: Year wise outbreak of Hendra virus in different regions of Australia [31]

S. No	State	year
1.	Mackay	1994
2.	Cairns	1999,2000
3.	Townsville	2004
4.	Barchester	2006,2007
5.	Clifton beach	2007
6.	Brisbane	1994,2008

Hendra virus outbreaks are seen several times in Australia since 1994. In 1994 first outbreak occurred in Mackay and Brisbane & in cairns in 1999 & later in 2004 in Townsville and cairns & outbreak in Clifton beach & Barchester in 2007 and there was an outbreak in Brisbane again in 2008. The fatality rate in horses is 80% and the fatality rate in humans is 60%. There have been only 7 human infections hence making the characterization of clinical features is less well understood [33].

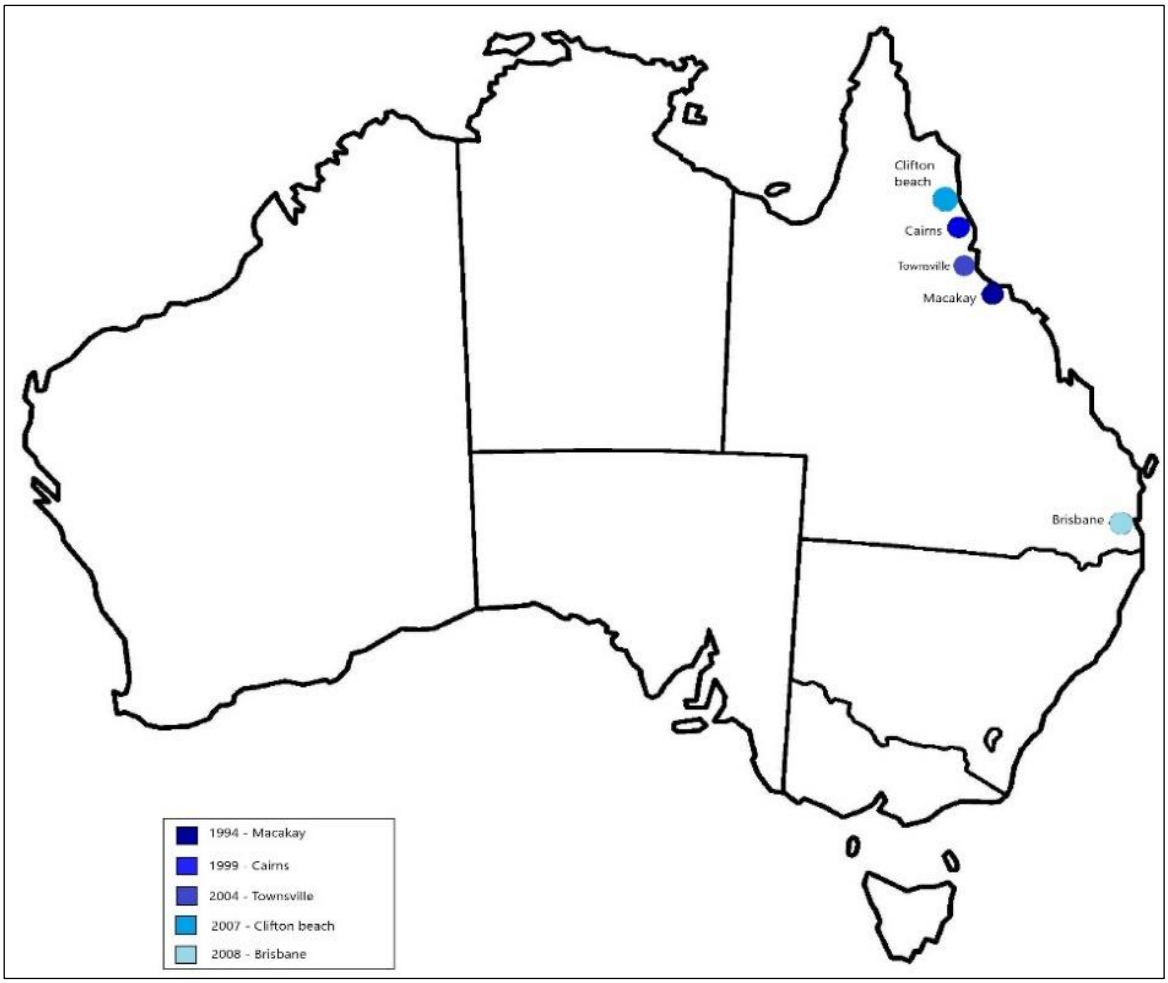

Figure 1: Pictographical presentation of Hendra viral outbreaks in Australia

In humans, the symptoms range from mild influenza-like illness to fatal respiratory illness with incubation period ranging from 9 to 16 days [29]. Clinical presentations can be divided into 3 categories viz, respiratory - tachypnea, with or without frothy nasal discharge, neurological - ataxia, head tilt, seizures, urinary incontinence, circling, recumbency, altered mental health, and others - depression, tachycardia, anorexia, fever, and restlessness. Initially, it starts with fever, cough, sore throat & headache and progresses into varied symptoms like meningitis and encephalitis, etc [33].

Pathogenesis in horses, the incubation period in horses ranges from 4-16 days. In horses it has been observed that both neurological and respiratory signs have been a feature of HeV infection. This virus can cause fatal within 48-75 hours in horses.

In horses, it has been observed that both neurological and respiratory signs has been a feature of HeV infection. In humans, after the entry of the virus into the body it can affect the respiratory system and CNS. It can enter into the CNS by choroid plexus or by cerebral blood vessels. HeV can efficiently infect epithelial cells of the lower respiratory tract and replicate to higher titers. Human-to-human transmission is observed at symptomatic stages. Hendra virus infection on respiratory tract epithelium results in induction of inflammatory cytokines and also key inflammatory mediators such as IL-6, IL-8, IL-1 ALPHA, MCP-I, G-CSF, GM-CSF. which result in recruitment of immune cells and can progress to acute respiratory distress syndrome (ARDS). Infection in the lower respiratory tract can cause an inflammatory response depending on the site of infection.

During the late stage of disease, virus replication spreads from the respiratory epithelium to the endothelium of lungs and this infection triggers a prominent vasculitis in small vessels and capillaries as characterized by endothelial syncytium and mural necrosis. In severe cases, the lungs will show gross lesions of congestion hemorrhage. The primary target is the bronchial epithelium and type-II pneumocytes. HeV can enter the bloodstream and disseminate throughout the host in either in free form or by binding to the host's leucocytes. In addition to the lungs, other organs that HeV can target are liver, spleen, brain, and kidneys leading to multi-organ failure/ Multi Organ Dysfunction Syndrome (MODS). Hendra virus infection has been shown that bind to CD 3+ leucocytes without entry or

replication of the virus. The virus invades CD3+ cells, which has main function of cell mediated immunity involving in recognition of antigens, and thereby immunity is altered.

Infection in CNS is characterized by vasculitis, thrombosis & plaques found in white and grey matter. The experimental studies showed that the Hendra virus directly enters into CNS via the olfactory route [34]. Hendra virus can cause disruption of BBB (blood-brain barrier) and expression of pro-inflammatory mediators such as TNF- α and IL-1 β which is released by microglia. These pro-inflammatory mediators increase BBB permeability and induces neural cell injury and death. Disruption of BBB can be caused by two pathways viz, Viral replication in the microvasculature & by pro-inflammatory mediators [34].

There is no particular cure or approved license for treatment for the Hendra virus in humans and the patients are treated with supportive treatment or in Intensive care. Ribavirin is well known first-line treatment strategy for suspected viral infection. Ribavirin exhibits antiviral activity against a wide variety of both DNA/RNA viruses. Treatment with ribavirin in Malaysia in 1998 was reported to reduce mortality by 36%. In 2009, 3 individuals suspected of Hendra virus are given with Ribavirin + chloroquine of which all 3 people survived while the infection was not confirmed & hence this treatment is confirmed to be evident enough to support its usage [35].

Equivac® is the vaccine that is used for horses [36]. HeV- sG -V vaccine is the vaccine used for both Hendra and Nipah virus and is programmed with the global partnership between Auro vaccines, PATH, CEPI. The vaccine was originally developed by Dr. Christopher Broder & Dr. Katherine Bossart at the U.S government uniformed services university of health sciences. This vaccine contains G-glycoprotein of Hendra virus [35].

HeV - sG -V has shown good results in preclinical studies and is licensed to AURO vaccines Ltd. A first-in-human, phase – I trial is to be conducted in healthy adults of age above 18 to below 45 years in which patients with other diseases and pregnant women are excluded& study design being randomized, placebo-controlled, observer-blind, phase – I. The study plans to accrue eligible subjects into 3 successive dosage escalation cohorts consisting of 12,72,108 subjects. The three doses planned for study are 10mcg, 30 mcg, and mcg. First cohort subjects will receive two doses of investigation product (IP) at the 28-day interval upon randomization as 5:1 ratio, of which, 10 receives two doses of HeV- sG -V 10 mcg, and 2 subjects will receive placebo. In the second cohort, subjects will be randomized in a 5:5:2 ratio with 30 receiving a 30mcg dosage on visits 1 and 2 i.e., at day 1 and 8 with placebo on visit 3 i.e., on day 29, and 30 receiving a 30mcg dosage of the vaccine on visit 1 and 3 with placebo on visit 2, while the 12 subjects will receive placebo on every visit. The third cohort will be randomized in 5:5:5:3 so that subjects are assigned to each of the three possible different regimens consisting of 100 mcg dosage of vaccine and placebo administered. 1st group (30 subjects) will receive HeV- sG -V on visit 1 and placebo on visits 2 & 3, 2nd group (30 subjects) with HeV- sG -V on visits 1 & 2 and placebo on visits 3, 3rd group (30 subjects) will receive HeV- sG -V on visits 1& 3 and placebo on visits 2. While the remaining 18 will receive a placebo on every visit [37].

4. CRIMEAN CONGO HEMORRHAGIC FEVER (CCHF)

Crimean Congo Haemorrhagic Fever (CCHF) is a viral haemorrhagic fever transmitted by ticks. CCHF can also be contracted through contact with viraemic animal tissues during and just post slaughter of animals. CCHF is caused by a tick-borne virus (Nairovirus) which belongs to the Bunyaviridae family. CCHF is endemic in Africa, The Balkans, The Middle East and in Asia. The fatality rate is about 10% - 40% [38, 39].

CCHF circulates in nature in a cycle between 2 hosts of ticks and non-human vertebrates and poses a threat to public health as it is highly pathogenic to humans. The bite of infected Ixodid ticks (especially Hyalomma spp) causes infection to humans. This can also be due to direct contact with blood or tissues of viraemic animals or patients. Hyalomma spp. ticks mainly *H.marginatum, H.rufipes, H.anatolicum and H.asiaticum* are the main competent vectors of the virus [40]. The CCHF virus hosts can include wide range of animals like sheep, cattle, goats etc. Mostly birds are resistant to this virus, but Ostriches can contract this infection. Animals are infected by tick bites and the virus enters blood stream and it remains there for about a week after which can thereby allow the cycle to continue. There are various tick genera which can be infected but the Hyalomma genus ticks are principal vectors [39].

CCHF is transmitted either by tick bites or by contact with infected animal blood or tissues immediately after slaughter. Cases are mostly observed in people of livestock industry, agricultural workers, veterinarians, slaughterhouse workers etc [39].

The CCHF was first discovered during an outbreak in Crimea in 1944, and later the causative agent was identical to virus isolated from patient in Congo in 1956. Hence the name Crimean Congo Hemorrhagic Fever was given. The disease is endemic in many regions like Africa (Democratic Republic of Congo, Uganda, Mauritania, Nigeria, South Africa, Senegal and Sudan), Europe (Russia, Bulgaria, Kosovo, Turkey, Greece, Spain), Middle East (Iraq, Iran, Kuwait, Saudi Arabia, Oman, UAE), Asia (China, Kazakhstan, Tajikistan, Uzbekistan, Afghanistan, Pakistan, India). *Hyalomma marginatum* is the principal vector in Europe. *Hyalomma asiaticum* is the principal vector in Asia. In the year

2006, *Hyalomma marginatum* first detected in Netherlands and south Germany & *Hyalomma antollicum* ticks first seen in India in 2011 [41].

Among the tick-borne viruses that affect human health, CCHF virus has the most extensive geographic range, and among the medically important arboviruses, it is the second most widespread disease. There have been nearly 140 outbreaks all over the world of which more than 5000 cases are reported. A total of 52 countries have been identified as endemic or potentially endemic regions. In the initial years, CCHF cases were seen in former Soviet Union (Crimea, Astrakhan, Rostov, Uzbekistan, Kazakhstan, Tajikistan) and Bulgaria. But later on, parts of Africa like Democratic Republic of Congo, Uganda, Mauritania are the areas where outbreaks were seen. The Middle East countries have also reported cases including Iraq, UAE, Saudi Arabia. In the last 10 years, most cases were from Pakistan, Iran, Bulgaria, Turkey and also India. Most of the outbreaks seen are in community and also contact with livestock affected by ticks is observed. In some cases, it is healthcare associated spread, like contact with blood and other body fluids of patients was the mode of transmission. When the recent outbreaks of CCHF infections are considered from the year 2008 – 2011, they were seen in Bulgaria, Sudan, Turkey, Iran, Kazakhstan, Tajikistan, and India. About 730 cases were reported, of which 57 deaths were reported. And out of this, around 16 were healthcare associated CCHF infection including 13 fatal cases [42]. Among the number of infected and fatal CCHF cases reported to PROMED between the years 1998 and 2013, a total of around 21 countries were involved. The overall CCHF infected patients were about 3246, including 451 deaths and CFR (Case Fatality Rate) of 13%. Of the given information, the most number of cases were seen in Turkey (1406), Russia (891), Iran (323), Pakistan (230) and Afghanistan (61). In terms of fatality, Turkey at the top of the table with 140 fatal cases followed by Pakistan (92), Iran (38) and Russia (33). Among the countries with most infected cases, the lowest fatalities were reported from Russia (4%) and Turkey (10%) [43].

If we consider the CCHF cases from different regions which were reported to medical literature, it has been put into four regions namely Africa, Asia, Europe, and Middle East. According to the literature, the most cases are from year before 2000 and also from 2000 – 2009, the most CCHF cases per annum were reported in Europe, followed by Middle East [44].

In case of CCHF virus, there is sudden onset of symptoms. This includes fever, muscle ache (myalgia), dizziness, neck pain, stiffness of neck, headache, backache, sore eyes and sensitivity to light (photophobia). These symptoms are followed by nausea, vomiting, diarrhoea, abdominal pain, sore throat, mood swings and confusion. Excessive sleeping, dizziness, weakness and abdominal pain in the upper right quadrant, liver enlargement (hepatomegaly) can be observed after about 2 – 4 days of illness [45].

Tachycardia, petechial rash on internal mucosal surfaces, lymphadenopathy, etc maybe the other clinical signs. The petechiae may in turn lead to large rashes called ecchymoses and other conditions like melena, haematuria, nasal bleeding (epistaxis) and gum bleeding. Kidney damage or deterioration, hepatitis and sudden hepatic or pulmonary failure can be observed after fifth day of illness. Mortality is about 30% in CCHF which is seen mostly in second week of illness. The patients who recover will gradually come to stable condition on ninth or tenth day [45].

CCHF virus is a widely distributed virus but there is limited information known about the pathophysiology. This is due to the bio safety necessity that is highly required for handling of virus. The present information is been concluded based on the autopsies, liver biopsies & blood analysis of patients [46].

Viral entry- As we all know, in almost all the cases, epithelium is the first barrier. After the tick bite, the viral proteins settle in basolateral membrane that leads virus into blood stream. The entry into host cells is by binding of envelope glycoprotein Gc to cell surface-associated receptors. The bite of tick helps virus entry into vascular system but spread of virus to body is not exactly known. The virus can be moved to or transported to lymph nodes, spleen etc. There will be increase in number of virus in macrophages and dendritic cells also. This passes on to systemic circulation of host. As per the studies based on animal models, the virus amplifies in liver, spleen & blood initially and then spreads all over to the kidneys, brain and lungs. Firstly, replication occurs in blood and then in liver, spleen as days pass. The brain is affected at much later stages of infection. There can also be entry of the virus into the blood – CSF barrier. Transmission of the virus to the cerebrospinal fluid (CSF) was demonstrated in other viral hemorrhagic fevers as a result of increased vascular permeability by cytokine release and subsequently disruption of the blood–CSF barrier and cause disturbances in it [46].

Endothelial damage and increase in vascular permeability – The main target of the virus is the epithelial cells and thus the characteristics of CCHF like haemorrhage and vascular permeability. Activation of epithelial cells is a critical step involving the leukocytes. The chain of reactions can start due to the endothelium damage. It can be done directly by virus or by virus-induced host derived soluble mediators indirectly. Soluble mediators like E-selectin, Vascular cell Adhesion Molecule-1 (VCAM-1), Intercellular Adhesion Molecule-1 (ICAM-1) and leukocyte adhesion takes place, which indicates vascular damage. The release of various cytokines like IL-1, IL-6, IL-8, IL-10, TNF-α contribute in CCHF progression. The cytokines are released from epithelial cells and also from the

macrophages and dendritic cells affected by CCHF virus. The soluble mediators increase action and release of ICAM-1. Excess release of cytokines leads to complications and endothelial damage. The process of CCHF resembles sepsis leading to systemic vascular collapse. As the epithelial cells release mediators, it leads to increased permeability. Vascular leakage occurs due to TNF-α, because of microtubule weakening [46].

Immune response impairment and delayed induction of Interferons – The natural immune response or innate immunity of our body acts against the viruses but in case of CCHF, the natural immunity is disturbed and taken into control, which helps in further replication of virus. In case of acquired immunity, macrophages and dendritic cells play an important role by release of cytokines. But as virus attacks, it disturbs the macrophages, dendritic cells and also the MHC-II complex which prepares T cells. Usually, interferons play a crucial role which provides antiviral response of natural immunity. They inhibit proliferation of cells, apoptosis regulation, and immunomodulation and help in controlling spread of infection. But CCHF virus are IFN-sensitive viruses and delays production of IFN's [46].

Decreased NK cells and lymphocytes - The function of NK cells and lymphocytes is to detect the virus and lysis of cells. It plays a major role in natural immunity. Studies show that there is initial increase of B and T lymphocytes, NK cells because of infection, but there is decline in its production leading to decrease in its levels as infection progress. So, both innate as well as acquired immune system functions are depleted leading to increase in replication of virus [46].

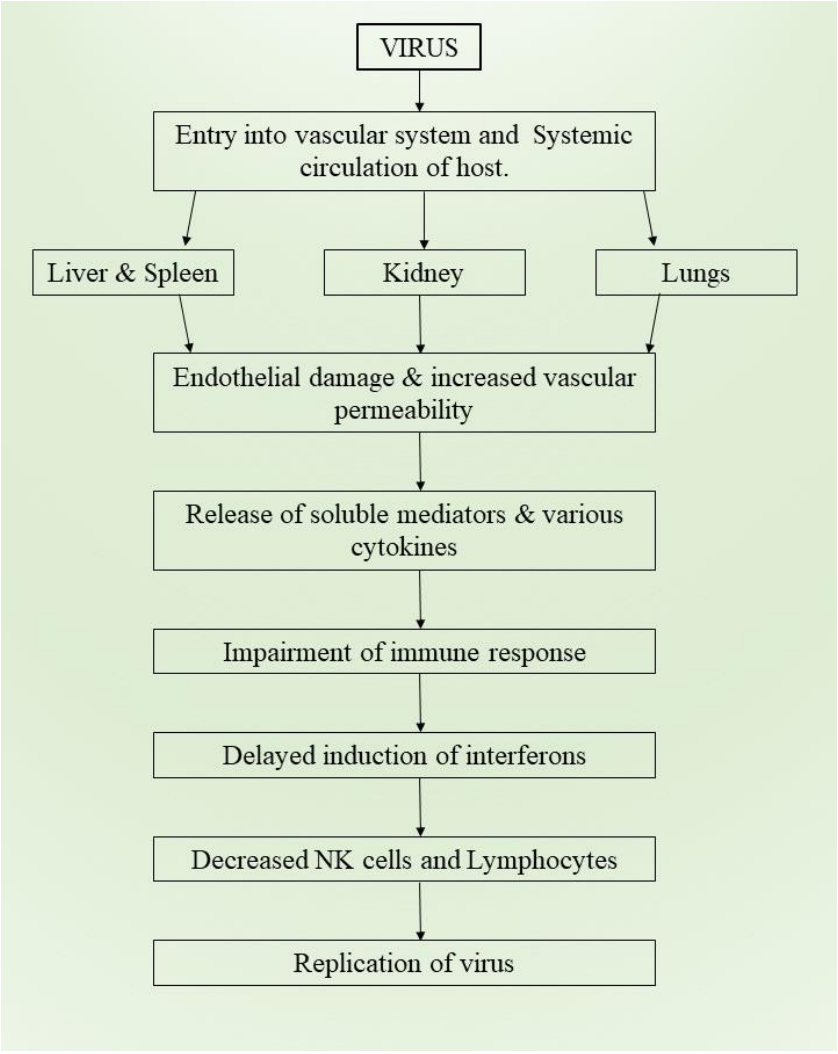

Figure 2: Pathophysiology of CCHF virus in humans

There is no specific treatment or therapy for CCHF that has been proven to be efficient and giving desired results. It is extremely important to look into all possible causes of symptoms. After performing the diagnostic tests, broad spectrum antibiotics can be given. To control and decrease healthcare associated infections, preventive measures should be taken. Supportive therapies are crucial to improve haemostasis etc. Maintenance therapies like hydration, blood transfusion, and other specific supportive therapies should be started as soon as possible. If in case Disseminated Intravascular Coagulation (DIC) is found, treatment becomes more

complicated, as it exhibits a natural tendency to bleed. In patients with VAHPS (Virus-associated haemophagocytic syndrome), Methylprednisolone of high doses showed significant activity. But its use and administration are still observational [47].

Ribavirin is the drug of choice and the only drug used in treatment of CCHF. The MOA of ribavirin is to inhibit replication of CCHF virus. It can be administered orally or by i.v route. In treatment of many patients, ribavirin was included but its efficacy is not yet assessed properly and effective results are not obtained. Ribavirin is a choice of drug for patients with CCHF in the early phase of illness and should be administered as early as possible. Neurological abnormalities and haematological abnormalities are some of the side effects observed when ribavirin upon administration. Ribavirin is mostly indicated in early stages i.e., pre- haemorrhagic stage because this is the phase when viraemia is highest. It is usually contraindicated in pregnant women [47, 48]. Antimicrobials are usually not recommended in confirmed cases of CCHF but if there is super infection observed, then they can be considered. Glucocorticoids efficacy in CCHF treatment is not yet confirmed. But studies have shown that the administration of Methylprednisolone promotes haematological recovery, reverse haemorrhagic lesions and reduce need for blood product transfusion [48]. Interferon-α has been reported as the one which helps in inhibition of CCHF virus growth in endothelial and hepatoma cells of humans. It is considered as a major factor acting against the IFN-induced MxA, which is induced exclusively by α and β IFNs and belongs to the dynamin superfamily of large GTPases, is a major factor mediating the antiviral effect against CCHFV. The MxA (Myxovirus resistance protein A) interacts with nucleocapsid protein and therefore inhibits replication of cells. IFN therapy in patients suffering from CCHF is not yet established or finalised and is only experimental for patients with CCHF. So, IFN therapy is not recommended and stopped due to its severe side effects [47].

The intravenous transfer of immunoglobulin active against CCHF virus can be considered as an effective treatment. In this the immunoglobulin products are prepared from sera collected from survivors and used. This can be widely available in future and studies have to be still carried out [47].

There is no globally recognised vaccine for CCHF virus. But since 1974, a vaccine that has been used in Bulgaria (Originated in Union of Soviet Socialist Republics-USSR is prepared from CCHF virus infected mice brain tissue, and administered subcutaneously due to which a decrease in cases is observed. Because of lack of efficacy trials on this vaccine, it is not an option for worldwide use [49].

The CCHF vaccine search has accelerated in recent years, and is based on animal models. The CCHF vaccine approaches include subunit antigen preparations, DNA and viral vectors, genetically modified plants, mRNA vaccines etc [49]. Scientific and Technological Research Council of Turkey in collaboration with CRO conducted interventional, phase- I studies on biological CCHF vaccine (KIRIM-KONGO-VAX) [50].

5. SWINE INFLUENZA (SWINE FLU)

Swine flu or swine influenza is an infection caused by one of the types of swine influenza viruses. It is the strain of influenza family of viruses that is endemic in pigs. Swine influenza virus (SIV) is common throughout worldwide pig populations. Also known as swine/variant influenza. In humans, the transmission is not so common from pigs, and this does not always lead to human flu. If transmission occurs, it is called Zoonotic swine flu [51].

Swine influenza is caused by type A influenza virus, a respiratory disease of pigs that regularly causes outbreaks of influenza in pigs. The viruses usually do not infect humans, but rare infections are seen. The virus that infects humans are called variant viruses. This happens when people are exposed to infected pigs. Cases of limited person-to-person spread of variant viruses are reported [52]. The viruses change constantly like other influenza/human viruses. When influenza viruses from different species infect pigs, the viruses can swap genes and new viruses emerge. Three main types of influenza A virus subtypes are isolated in pigs i.e., H1N1, H1N2, H3N2. It can spread through close contact, either from contaminated objects between infected and uninfected pigs. Infected swine herds, and those vaccinated against swine flu, may have sporadic disease or they may show mild or no symptoms of infection even after vaccination [51].

Swine flu was initially seen in the United States in April, 2009, where the strain of particular virus was mixture of three types of strains. Six of the genes were very similar to H1N2 influenza virus that was found in pigs in the year 2000 [53]. This virus was reported to as swine flu because laboratory tests showed that its gene segments were similar to influenza viruses that were identified and circulated among pigs & resulted from swapping of genes i.e., reassortment [53].

In 1930's, swine flu was first isolated from pigs in the United States and was then recognised as a cause of flu infection in pigs by pork producers and veterinarians, and it has been the predominant swine influenza strain for the next 60 years. Infection was known to develop in people who are in close contact with pigs and even the pigs are affected by human flu. This causes cross species transmission of virus and is limited to a particular area but not caused globally. But due to the genetic variations, there is always a choice of cross-species transmission of virus. The "2009 swine flu" strain, was termed as novel H1N1 flu, because it was predominantly infecting humans and has two main

surface antigens haemagglutinin type-I and neuraminidase type-I. There are eight strands of RNA in this, of which one is from human flu strains, two from avian strains and five from swine strains. According to Centre for Disease Control and Prevention (CDC), there has been an estimate of 43-89 million cases of swine flu during one year span, including 1799 deaths and 178 countries infected worldwide. In 1918, the deadly influenza pandemic of H1N1 influenza virus caused infection in 500 million people approximately all over the world including deaths of around 50-100 million people [54].

The H1N1 variant is a descendant of the 1918 swine flu pandemic strain. These usually are seen in pigs but can also affect humans. The swine are the potential reservoirs of flu virus and could persist and emerge to re infect humans once the immunity to the strains is decreased(54). The virus has infected more than 60 million people in the United States from April 2009 to April 2010, according to CDC. These infections led to around 274,000 hospitalisations and 12,500 deaths with a fatality rate of 0.02%. About 151,700 to 575,400 people have lost their lives because of that flu worldwide, as per CDC estimation. The flu mainly affected children and young to middle-aged adults. All over the world, 80% of the deaths were seen in people below the age of 65 [55]. The WHO, declared swine flu as a pandemic\officially in August, 2010 after being declared as pandemic in August, 2009(51). Recently in 2015, a mutant H1N1 strain which caused global pandemic in 2009, was seen all across India which gave rise to more than 10,000 cases and resulting in 774 deaths. The people who are at more risk of this infection are the children of age less than 5 years, adults of more than 65 years of age, children below 19 years of age on long term use of aspirin therapy, immunocompromised patients, and people with various chronic diseases [54].

The signs and symptoms of Swine influenza are very much similar to those of seasonal influenza. The patients are presented with symptoms of acute respiratory illness mainly that includes fever, cough, sore throat, headache, chills, fatigue, diarrhoea, nausea and vomiting [56].

The duration of illness can be mostly for about four to six days. The infection period can be considered from one day before onset of symptoms to seven days after onset of symptoms. Signs of apnoea, tachypnoea, dyspnoea, dehydration, irritability, cyanosis and altered mental status seen in children and if they are hospitalised for swine flu then neurological complications are common and can be fatal too. Seizures, encephalopathy, disorientation, loss of consciousness are some of the neurological complications reported [56].

H1N1 swine influenza is an acute disease. This usually affects the upper respiratory tract, and in some cases the lower respiratory tract too resulting in inflammation [54]. The influenza viruses of A, B, C types are enveloped RNA viruses with segmented genome. In short, it is present as eight different RNA segments and not as single stranded. A human/bird influenza virus has the capability of affecting and infect a pig respiratory cell like the swine influenza virus. The strands of an enveloped swine influenza virus can be enclosed with strands of human virus too. There can be a new subtype of virus formation because of different RNA segments combination, known as antigenic shift, that shows the characteristics of swine influenza virus and can still affect humans [57].

This virus mainly targets the respiratory cells of humans. It enters into the body and the respiratory cells and slowly starts damaging the respiratory tract lining, which leads to inflammation and swelling of respiratory tract. The virus structure is such that, it is covered by a protein coat and lipid envelope. The lipid envelope consists of glycoproteins which are embedded in the surface, namely neuraminidase and haemagglutinin. After the entry of virus into the respiratory tract, it binds to receptors on the surface of epithelial cells through haemagglutinin onto sialic acid sugars [58]. The virus is separated out and spreads into the respiratory secretions. Then, the virus binds to respiratory epithelial cells in trachea and bronchi and penetrates through it. From the lungs, it passes into blood through cells of alveoli having capillary network. Then, the virus acts on B-lymphocytes and B-cells, which in turn leads to depletion in its activity resulting in decrease of immune activity/ immunity [58].

In the treatment of swine influenza, firstly there should be implementation of infection control precautions to decrease the disease spread and also to treat severe illness and death. Antiviral prophylaxis must be provided to healthcare professional involved in case management. Mainly, there are two groups of antiviral drugs used to treat cases of influenza. The two groups are Adamantanes (Amantadine, Rimantadine) and Neuraminidase inhibitors (Zanamivir, Oseltamivir, Peramivir, Laninamivir). Of the mentioned drugs, most of the drugs are available and licensed in all countries except some (Peramivir, Laninamivir). Both group of drugs are effective but also many have some side effects. The efficiency of antiviral drugs is more if administered within two days of onset of symptoms & can be used in severe cases too. Antiviral resistance is one of the drawbacks that can emerge during treatment. In one of the studies, it was proven that around 9% of swine influenza viruses gained resistance against neuraminidase inhibitors are H1N2, H3N2 and H9N2 [59].

The drugs of neuraminidase inhibitors group Zanamivir and Oseltamivir are known to show efficient activity against both, influenza A and influenza B. Zanamivir is given as dry powder for inhalation for uncomplicated influenza A or B can be used by patients of age 7 years or more and also who has been

symptomatic for less than 48 hours. It is also approved for prophylaxis of influenza in 5 years or older patients.

Oseltamivir is given as an oral capsule given in case of uncomplicated influenza A or B to patients of age one year or more and also those who are symptomatic for less than 48 hours. This can also be given in case of prophylaxis. Oseltamivir is well tolerated and can be used and preferred in both prophylaxis and treatment. Gastrointestinal side effects are seen usually in cases of increased dose (more than 300mg/day). Other side effects are insomnia, bronchitis, vertigo, skin rashes etc. The general dosing of oseltamivir is 30 mg-75 mg twice daily for 5 days (according to weight), 12 mg-25 mg twice daily for 5 days (according to age) and syrup of 12 mg per ml [59].

Supportive therapy includes fluid administration and rest, nutrition, oxygen therapy, vasopressors for shock. For some cases, it can be inclusion of drugs such as antibiotics etc. to treat secondary infections. In case of myalgia, fever, headache, Ibuprofen or paracetamol can be given. If patient had signs of dyspnea, tachypnea and oxygen saturation is less than 90%, then they should be provided with oxygen therapy. Mechanical ventilation is necessary in case of acute respiratory failure and blood oxygen below 90% and partial pressure of oxygen if less than 60 mm Hg. Airway, Breathing, Circulation should be maintained along with electrolyte balance and nutrition. Immunomodulating drugs are not found to be beneficial and also high dose corticosteroids have no evidence of benefits. Corticosteroids in low doses maybe used in case of sepsis shock [59].

There are a variety of flu vaccines with different levels of safety and effectiveness. There are two major rollouts for swine flu in 1976 and 2009. The vaccines of 1976 was in response to emergence of virus at Fort Dix. and a few vaccines were approved by FDA [60].

Table 7: List of H1N1 2009 Monovalent vaccines with its approval status and manufacturer details [61]

Name	Manufacturer	Approved for
Influenza A(H1N1) 2009 Monovalent vaccines	CSL Limited	Use in persons of age 6 months or older.
Influenza A(H1N1) 2009 Monovalent vaccines	Med Immune LLC	Use in persons aged 2 – 49 years.
Influenza A(H1N1) 2009 Monovalent vaccines	ID Biomedical Corporation of Quebec	Use in persons of age 18 years or above.
Influenza A(H1N1) 2009 Monovalent vaccines	Sanofi Pasteur, Inc.	Use in persons of age 6 years or above.
Influenza virus vaccine Trade name – Flulaval	ID Biomedical Corporation of Quebec	Influenza of subtype A and B for 6 months of age or above.

Table 8: H1N1 vaccines in clinical trials [62]

Sponsor	Study type & Phase	Intervention / Observation
Sanofi Pasteur, a Sanofi company	Interventional, Phase - II	Biological: Swine A/H1N1 influenza vaccine (split virion, inactivated) Biological: Swine A/H1N1 influenza vaccine (split virion, inactivated + adjuvant)
Novartis Vaccines	Interventional, Phase - IV	Biological: Emulsion, cell culture- based, influenza HA vaccine H1N1.
Sanofi Pasteur, a Sanofi company	Observational study	For safety and efficacy of Humenza and Panenza vaccines.
Sanofi Pasteur, a Sanofi company	Interventional, Phase - II	Biological: Swine A/H1N1 influenza vaccine (split virion, inactivated) Biological: Swine A/H1N1 influenza vaccine (split virion, inactivated + adjuvant) Biological: Swine A/H1N1 influenza vaccine (split virion, inactivated + adjuvant)

CONCLUSIONS

Despite the evidence on the advancement and development of various treatments and vaccines against viral outbreaks, as detailed in this review, the outbreaks are still seen in major epicenters resulting in its devastating sequel. This intrigues a major concern on our responses & preparedness to the outbreaks. Regulations or policies are to be laid to confine the viral infection by imposing restrictions when seen in a group of population, thereby preventing its outbreak. However, such regulations are in place, we still face the outbreaks indicating a lacunae in the policies. The government agencies should also be prepared with management of outbreaks well in advance to reduce the mortality.

Acknowledgment

I would like to convey my sincere gratitude to Dr. Chandrasekhara Rao Baru, Professor & Principal, Chilkur Balaji College of Pharmacy for supporting & encouraging the students to take part in research projects.

Conflict of interest: None declared by the authors.

Funding statement: The current project did not receive any financial benefits or funding or grants from any organization or institution.

Author contribution:
Dr. Nithish Sattoju: Literature Review, Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing, Supervision.
Pranay Reddy R: Literature review, Writing - original draft
Vinay Surisetty: Literature review, Writing - original draft

REFERENCES

1. Measles [Internet]. [cited 2022 Nov 28]. Available from: https://www.who.int/news-room/fact-sheets/detail/measles
2. Measles - Symptoms and causes - Mayo Clinic [Internet]. [cited 2022 Nov 28]. Available from: https://www.mayoclinic.org/diseases-conditions/measles/symptoms-causes/syc-20374857
3. Transmission of Measles | CDC [Internet]. [cited 2022 Nov 28]. Available from: https://www.cdc.gov/measles/transmission.html
4. Measles History [Internet]. [cited 2022 Nov 28]. Available from: https://www.news-medical.net/health/Measles-History.aspx
5. History of Measles | CDC [Internet]. [cited 2022 Nov 28]. Available from: https://www.cdc.gov/measles/about/history.html
6. Leung AKC, Hon KL, Leong KF, Sergi CM. Measles: a disease often forgotten but not gone. Hong Kong Med J [Internet]. 2018 Oct 1 [cited 2022 Nov 28];24(5):512–20. Available from: https://pubmed.ncbi.nlm.nih.gov/30245481/
7. Naim HY. Measles virus. https://doi.org/104161/hv34298 [Internet]. 2015 Jan 1 [cited 2022 Nov 28];11(1):21–6. Available from: https://www.tandfonline.com/doi/abs/10.4161/hv.34298
8. Kondamudi NP, Waymack JR. Measles. StatPearls [Internet]. 2022 Aug 14 [cited 2022 Nov 28]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK448068/
9. Rubeola (Measles) - StatPearls - NCBI Bookshelf [Internet]. [cited 2022 Nov 28]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557716/
10. Strebel PM, Orenstein WA. Measles. Solomon CG, editor. https://doi.org/101056/NEJMcp1905181 [Internet]. 2019 Jul 10 [cited 2022 Nov 28];381(4):349–57. Available from: https://www.nejm.org/doi/10.1056/NEJMcp1905181
11. Measles Vaccination CDC [Internet]. [cited 2022 Nov 28]. Available from: https://www.cdc.gov/vaccines/vpd/measles/index.html
12. Pediatric Vaccines: Global Brands and Country Availability: Introduction, Hepatitis B Virus (HBV) Vaccine, Pneumococcal Conjugate Vaccines (PCVs) [Internet]. [cited 2022 Nov 28]. Available from: https://emedicine.medscape.com/article/2500038-overview#a5
13. Vaccine, MMR brands in India DrugsUpdate India [Internet]. [cited 2022 Nov 28]. Available from: https://www.drugsupdate.com/brand/showavailable brands/560
14. Avian influenza in humans National Health Portal Of India [Internet]. [cited 2022 Nov 24]. Available from: https://www.nhp.gov.in/disease/communicable-disease/avian-influenza-in-humans
15. Transmission of Avian Influenza A Viruses Between Animals and People | Avian Influenza (Flu) [Internet]. [cited 2022 Nov 24]. Available from: https://www.cdc.gov/flu/avianflu/virus-transmission.htm
16. Information on Bird Flu Avian Influenza (Flu) [Internet]. [cited 2022 Nov 24]. Available from: https://www.cdc.gov/flu/avianflu/index.htm
17. Bird Flu Virus Infections in Humans | Avian Influenza (Flu) [Internet]. [cited 2022 Nov 24]. Available from: https://www.cdc.gov/flu/avianflu/avian-in-humans.htm
18. Avian Influenza. New Hampshire Department of Health and Human services [Internet]. [cited 2021 Oct 23]. Available from: Avian Influenza. New Hampshire Department of Health and Human services
19. Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2021, 15 April 2021 [Internet]. [cited 2022 Nov 24]. Available from: https://www.who.int/publications/m/item/cumulative-number-of-confirmed-human-cases-for-avian-influenza-a(h5n1)-reported-to-who-2003-2021-15-april-2021
20. Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2021 [Internet]. [cited 2022 Nov 24]. Available from: https://cdn.who.int/media/docs/default-source/influenza/h5n1-human-case-cumulative-table/2021_april_tableh5n1.pdf?sfvrsn=fc40672c_5&download=true
21. Influenza (Avian and other zoonotic) [Internet]. [cited 2022 Nov 24]. Available from: https://www.who.int/en/news-room/fact-sheets/detail/influenza-(avian-and-other-zoonotic)
22. Avian Influenza (Bird Flu): Background, Pathophysiology, Epidemiology [Internet]. [cited 2022 Nov 24]. Available from: https://emedicine.medscape.com/article/2500029-overview#a4
23. Korteweg C, Gu J. Pathology, molecular biology, and pathogenesis of avian influenza A (H5N1) infection in humans. Am J Pathol [Internet]. 2008

[cited 2022 Nov 24];172(5):1155–70. Available from: https://pubmed.ncbi.nlm.nih.gov/18403604/
24. Clinical Management of Influenza. [Internet]. [cited 2021 Oct 11]. Available from: https://www.who.int/influenza/resources/documents/ClinicalManagement07.pdf
25. Avian Influenza Vaccine - an overview | ScienceDirect Topics [Internet]. [cited 2022 Oct 21]. Available from: https://www.sciencedirect.com/topics/medicine-and-dentistry/avian-influenza-vaccine
26. Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted | FDA [Internet]. [cited 2022 Nov 24]. Available from: https://www.fda.gov/vaccines-blood-biologics/vaccines/influenza-h5n1-virus-monovalent-vaccine-adjuvanted
27. AUDENZ | FDA [Internet]. [cited 2022 Nov 24]. Available from: https://www.fda.gov/vaccines-blood-biologics/audenz
28. Search of: Vaccines | Avian Influenza - List Results - ClinicalTrials.gov [Internet]. [cited 2022 Nov 24]. Available from: https://www.clinicaltrials.gov/ct2/results?cond=Avian+Influenza&term=Vaccines&cntry=&state=&city=&dist=
29. Hendra Virus Disease | CDC [Internet]. [cited 2022 Nov 24]. Available from: https://www.cdc.gov/vhf/hendra/index.html
30. Hendra virus infection [Internet]. [cited 2022 Nov 24]. Available from: https://www.who.int/health-topics/hendra-virus-disease#tab=tab_3
31. Eaton BT, Wang LF. Henipaviruses. Encyclopedia of Virology. 2008 Jan 1;321–7.
32. Field HE. Hendra virus ecology and transmission. Curr Opin Virol [Internet]. 2016 Feb 1 [cited 2022 Nov 24]; 16: 120–5. Available from: https://pubmed.ncbi.nlm.nih.gov/26978066/
33. Yuen KY, Fraser NS, Henning J, Halpin K, Gibson JS, Betzien L, et al. Hendra virus: Epidemiology dynamics in relation to climate change, diagnostic tests and control measures. One Health [Internet]. 2021 Jun 1 [cited 2022 Nov 24];12. Available from: https://pubmed.ncbi.nlm.nih.gov/33363250/
34. Escaffre O, Borisevich V, Rockx B. Pathogenesis of Hendra and Nipah virus infection in humans. J Infect Dev Ctries [Internet]. 2013 Apr [cited 2022 Nov 24];7(4):308–11. Available from: https://pubmed.ncbi.nlm.nih.gov/23592639/
35. Broder CC, Xu K, Nikolov DB, Zhu Z, Dimitrov DS, Middleton D, et al. A treatment for and vaccine against the deadly Hendra and Nipah viruses. Antiviral Res [Internet]. 2013 [cited 2022 Nov 24];100(1):8. Available from: /pmc/articles/PMC4418552/
36. Hendra virus fact sheet - Fact sheets [Internet]. [cited 2022 Nov 24]. Available from: https://www.health.nsw.gov.au/Infectious/factsheets/Pages/hendra_virus.aspx
37. Safety and Immunogenicity of a Nipah Virus Vaccine - Full Text View - ClinicalTrials.gov [Internet]. [cited 2022 Nov 24]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT04199169#studydesign
38. Crimean-Congo haemorrhagic fever [Internet]. [cited 2022 Nov 28]. Available from: https://www.who.int/health-topics/crimean-congo-haemorrhagic-fever#tab=tab_1
39. Crimean-Congo haemorrhagic fever [Internet]. [cited 2022 Nov 28]. Available from: https://www.who.int/news-room/fact-sheets/detail/crimean-congo-haemorrhagic-fever
40. Papa A, Tsergouli K, Tsioka K, Mirazimi A. Crimean-Congo hemorrhagic fever: Tick-host-virus interactions. Front Cell Infect Microbiol. 2017 May 26;7(MAY):213.
41. Al-Abri SS, Abaidani I al, Fazlalipour M, Mostafavi E, Leblebicioglu H, Pshenichnaya N, et al. Current status of Crimean-Congo haemorrhagic fever in the World Health Organization Eastern Mediterranean Region: issues, challenges, and future directions. Int J Infect Dis [Internet]. 2017 May 1 [cited 2022 Nov 28]; 58: 82–9. Available from: https://pubmed.ncbi.nlm.nih.gov/28259724/
42. Appannanavar SB, Mishra B. An Update on Crimean Congo Hemorrhagic Fever. J Glob Infect Dis [Internet]. 2011 Jul [cited 2022 Nov 28];3(3):285. Available from: /pmc/articles/PMC3162818/
43. Ince Y, Yasa C, Metin M, Sonmez M, Meram E, Benkli B, et al. Crimean-Congo hemorrhagic fever infections reported by ProMED. Int J Infect Dis [Internet]. 2014 [cited 2022 Nov 28]; 26: 44–6. Available from: https://pubmed.ncbi.nlm.nih.gov/24947424/
44. Dowall SD, Carroll MW, Hewson R. Development of vaccines against Crimean-Congo haemorrhagic fever virus. Vaccine [Internet]. 2017 Oct 10 [cited 2022 Nov 28];35(44):6015. Available from: /pmc/articles/PMC5637709/
45. Crimean-Congo haemorrhagic fever (CCHF) : Symptoms, Diagnosis and Management - American International Medical University [Internet]. [cited 2022 Nov 28]. Available from: https://www.aimu.us/2016/12/20/crimean-congo-haemorrhagic-fever-cchf-symptoms-diagnosis-and-management/
46. Akinci E, Bodur H, Leblebicioglu H. Pathogenesis of Crimean-Congo hemorrhagic fever. Vector Borne Zoonotic Dis [Internet]. 2013 Jul 1 [cited 2022 Nov 28];13(7):429–37. Available from: https://pubmed.ncbi.nlm.nih.gov/23663164/
47. Crimean–Congo Hemorrhagic Fever and Future Perspectives [Internet]. [cited 2022 Nov 28]. Available from: https://www.medscape.com/viewarticle/735170_6
48. de la Calle-Prieto F, Martín-Quirós A, Trigo E, Mora-Rillo M, Arsuaga M, Díaz-Menéndez M, et al. Therapeutic management of Crimean-Congo haemorrhagic fever. Enfermedades Infecciosas y Microbiología Clínica (English Edition) [Internet].

2018 Oct 1 [cited 2022 Nov 28];36(8):517–22. Available from: https://www.elsevier.es/en-revista-enfermedades-infecciosas-microbiologia-clinica-english-428-articulo-therapeutic-management-crimean-congo-haemorrhagic-fever-S2529993X18301515

49. Tipih T, Burt FJ. Crimean-Congo Hemorrhagic Fever Virus: Advances in Vaccine Development. Biores Open Access [Internet]. 2020 May 1 [cited 2022 Nov 28];9(1):137–50. Available from: https://pubmed.ncbi.nlm.nih.gov/32461819/
50. Phase I Study to Evaluate Basic Pharmacodynamic, Pharmacological and Toxicological Effects of the Newly Developed Crimean-Congo Hemorrhagic Fever Vaccine for Humans - Tabular View - ClinicalTrials.gov [Internet]. [cited 2022 Nov 28]. Available from: https://www.clinicaltrials.gov/ct2/show/record/NCT03020771?term=Vaccines&cond=Crimean-Congo+Hemorrhagic+Fever&draw=2&rank=1&view=record
51. Key Facts about Swine Influenza (Swine Flu) in Pigs | CDC [Internet]. [cited 2022 Nov 28]. Available from: https://www.cdc.gov/flu/swineflu/keyfacts_pigs.htm
52. Key Facts about Human Infections with Variant Viruses | CDC [Internet]. [cited 2022 Nov 28]. Available from: https://www.cdc.gov/flu/swineflu/keyfacts-variant.htm
53. CDC [Internet]. [cited 2022 Feb 17]. Origin of 2009 H1N1 Flu (Swine flu): Questions and answers. Available from: https://www.cdc.gov/h1n1flu/information_h1n1_virus_qa.htm
54. Jilani TN, Jamil RT, Siddiqui AH. H1N1 Influenza. StatPearls [Internet]. 2022 Jul 18 [cited 2022 Nov 28]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK513241/
55. Fact check: Swine flu spread rapidly but was not as deadly as COVID-19 [Internet]. [cited 2022 Nov 28]. Available from: https://www.usatoday.com/story/news/factcheck/2020/08/13/fact-check-swine-flu-spread-rapidly-but-not-deadly-covid-19/5577001002/
56. H1N1 Influenza (Swine Flu) Clinical Presentation: History [Internet]. [cited 2022 Nov 28]. Available from: https://emedicine.medscape.com/article/1807048-clinical
57. Lokwani P, Kumar P, Upadhyay Y, Gupta S, Solanki R, Singh N. SWINE FLU: AN OVERVIEW.
58. Khan MZ GV. Epidemical Disease: A Review on Swine Flu. Int J Phar & Biomedical Research. 2015; 2: 9–11.
59. Rewar S, Mirdha D, Rewar P. Treatment and Prevention of Pandemic H1N1 Influenza. Ann Glob Health [Internet]. 2015 Sep 1 [cited 2022 Nov 28];81(5):645–53. Available from: https://pubmed.ncbi.nlm.nih.gov/27036721/
60. Swine flu vaccine: Safety, effectiveness, and side effects [Internet]. [cited 2022 Nov 28]. Available from: https://www.medicalnewstoday.com/articles/swine-flu-vaccine
61. Vaccines Licensed for Use in the United States | FDA [Internet]. [cited 2022 Nov 28]. Available from: https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states
62. Vaccines Swine Flu - List Results - ClinicalTrials.gov [Internet]. [cited 2022 Nov 28]. Available from: https://www.clinicaltrials.gov/ct2/results?cond=Swine+Flu&term=Vaccines&cntry=&state=&city=&dist=