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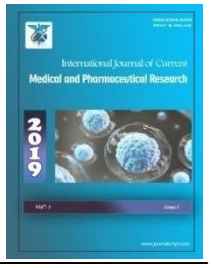

A REVIEW ON EMERGING VIRAL RESPIRATORY INFECTIONS

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ABSTRACT

Emerging viruses have caused a huge impact on mankind due to their unexpected occurrences at unusual time and place. Emergence of viral infections occur when etiological viruses cross their usual hide outs or borders. These viruses have awakened public awareness due to hype on various platforms, especially media. The reason for creating such explosive awareness is the impending high morbidity and mortality incurred by these viruses. Although most of them are non-vaccine preventable, early clinical diagnosis and palliative care with good infection control practices can prevent outbreaks and pandemics.

INTRODUCTION

Emerging infections are defined as ‘‘infections that have newly appeared in a population or have existed previously but are rapidly increasing in incidence or geographic range.’’[1]Viruses are the commonest emerging pathogens due to various factors such as human behavioral changes and migration, encroachment into wildlife habitats, wildlife trade, ecotourism, changes in agricultural practices etc.[2]An elaborate knowledge on all emerging viruses and their association to the respiratory tract is important since these viruses cause high morbidity and mortality. Respiratory involvement is very common in most of the emerging viral infections due to various reasons, commonest being their ability of human-human transmission through inhalation of infected droplets.

The list of emerging and re-emerging viruses released by the World Health Organization in 2005 is continual as many outbreaks and pandemics have occurred then after. An extended and updated list of emerging viral infections with respiratory involvement is elicited in table 1.

Global Impact of Emerging viral Infections[3]

During the past thirty years, over thirty new organisms were discovered worldwide, more than half of them being viruses. These organisms have originated at the level of human – animal interface and disseminate rapidly. They pose a huge threat to global health security since most of them do not have a cure. Healthcare providers also become victims to these infections during the course of diagnosis and treatment of infected individuals. Therefore, they have caused social and economic impact much greater in developing countries with fewer resources, Asia, unfortunately often being at the epicenter. With increasing travel, trade and frequent worldwide mobility of people, infections can easily cross international borders. Another major reason behind outbreaks and pandemics is their propensity to spread rampantly.

Influenza Viruses

There are four types of Influenza viruses (Influenza A, Influenza B, Influenza C, Influenza D). However, only Influenza A is of public health importance due to its potential of causing pandemics. Influenza A is further categorized based on its surface glycoproteins Hemagglutinin (H) and Neuraminidase (N) into various subtypes such as H1N1, H1N2, H2N3, H3N1, H3N2, H5N1, H5N6, H5N9, H6N1, H7N7, H7N9, H9N2, H10N8.Depending upon the host of origin, Influenza A viruses can be classified as Swine Influenza, Avian Influenza, other types of animal Influenza. Highly Pathogenic Avian Influenza (HPAI) viruses cause severe disease in poultry and result in high mortality rates, whereas Low Pathogenic Avian Influenza (LPAI) viruses cause mild disease in poultry. Seasonal Influenza is totally

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different from Avian / Swine Influenza viruses and the pandemics caused by them. All types of Influenza viruses are associated with respiratory infections and are described below in detail.

Avian Influenza (H5N1, H5N6, H5N9, H6N1, H7N7, H7N9, H9N2, H10N8)

Risk Factors: Bird species commonly susceptible to the virus arepigeon, geese, quail, ducks, poultry. Clinical suspicion should arise when individuals on presentation give history of handling these birds. Another susceptible population for acquiring H5N1 infection is children. Whereas H7N9 has been reported commonly in middle-aged and older men.[5,6]

Mode of Transmission: Direct or indirect contact with infected dead or live poultry or their secretions and fecal matter. Human to human transmission although rare can spread through inhalation of infected respiratory droplets.

Clinical Signs and Symptoms: There are variations in clinical presentation among people infected with different subtypes of Avian Influenza. Infection with H5N9 or H7N9 is known for its aggressive clinical course and high case fatality rate. H7N7 and H9N2 are known for their mild clinical course with documented fatal human infection with H7N7.H5N1 infections with fatal outcome have also been reported.[7] Incubation period is variable, H5N1 and H7N9 having an average incubation period of 5 days, seasonal Influenza having an incubation period of 2 days.

Common symptoms associated with Influenza viruses are high grade fever, cough, dyspnea. Upper respiratory tract involvement is uncommon. Other constitutional symptoms observed are diarrhea, abdominal pain, vomiting, chest pain, encephalitis. Complications may include pneumonia, super added bacterial / fungal infection, hypoxemic respiratory failure, septic shock. In children, fever, rhinorrhea, cough are common symptoms. Findings such as lymphopenia, thrombocytopenia and elevated transaminases are also common. Some children can present only with gastrointestinal symptoms.[8]

Swine Influenza (H1N1, H1N2, H2N3, H3N1, H3N2)

Risk Factors: People at risk of acquiring swine flu are children and pregnant women. Other risk groups include those with chronic lung disease, chronic cardiovascular disorders, chronic renal disease, chronic liver disease, neurological disorders and immunosuppression especially diabetes mellitus.[9,10]People working in pig farms and abattoirs where they come in close contact with secretions from dead or live pigs are at maximum risk of acquiring infection.

Mode of Transmission: Human to human transmission occurs through inhalation of infectious droplets from cough or sneeze of infected individuals. Surfaces contaminated with respiratory secretions and fomites also act as indirect means of transmission of the virus.

Clinical Signs and Symptoms: Case definitions have been proposed by the World Health Organization especially to define swine flu cases based on symptoms and diagnosis. Commonly reported symptoms of swine Influenza are: fever (in up to 80% cases) of about 100°F or higher and chills (in up to 60% cases), non-productive cough, sever body aches, nasal congestion, sneezing, headache (in up to 80% cases), chest discomfort. Sore throat is not common although might appear in few patients. All symptomsare rapid in onset and appear suddenly.[9]

Diagnosis of Influenza Viruses: Guidelines for diagnosis of Influenza viruses are put forth by the WHO and are followed uniformly worldwide. The basis of diagnosis could be as part of routine patient care or during outbreaks.[11]

Specimen Collection: Upper respiratory tract specimens – Nasal swab, throat swab, combined nasal and throat swab, nasopharyngeal aspirate, nasal wash, throat wash. All samples should be submitted in viral transport medium.

Lower Respiratory tract Specimens: Transtracheal aspiration, bronchoalveolar lavage, lung biopsy. Samples for molecular diagnosis of viral RNA should be collected in synthetic tip swabs (Dacron, polyester) and an aluminium or plastic shaft. Swabs which should not be used are those with cotton tips, wooden shaft and swabs made from calcium alginate.

Serum Samples: Two serum samples of 3-5ml each is mandatory. First sample is taken on longer than 7 days after onset of symptoms (acute phase). Second sample is taken 2-4 weeks after the first sample is sent (convalescent phase).

Samples for virus isolation should be immediately placed at 4°C after collection and transported in the Hank`s balanced salt solution. The diagnostic methods used to diagnose Influenza viruses are described in table 2.

Treatment of Influenza

Neuraminidase inhibitors are used as antivirals in treatment of Influenza virus. Four of this class of drugs namely are: Oseltamivir, Zanamivir, Peramivir and Laninamivir (long-acting). These drugs act by inhibiting the viral enzyme neuraminidase, thereby preventing its replication and its release from the host cells. These drugs have action against both Influenza A and B viruses. They are known to reduce mortality and complications. Effective antiviral activity is achieved when administered within 48 hours of onset of symptoms.[12]Minimum duration of treatment is 5 days which may extend in case of unsatisfactory clinical improvement. Oseltamivir is given at dose of 75 mg twice daily, Zanamivir is given at a dose of 10 mg twice daily. Intravenous fluids and parenteral nutrition is given as supportive therapy along with ventilator support, vasopressors wherever required. Antipyretics can be used, salicylates are avoided, secondary bacterial infections are treated with antibiotics.

Prevention of Influenza

Chemoprophylaxis: Chemoprophylaxis is given to close contacts, health care workers at high risk of exposure and other susceptible individuals. Oseltamivir is given as prophylaxis for individuals over 3 months of age for a duration of 7 days at a dose of 75 mg once daily. Zanamivir is preferred as prophylaxis only for use in more than 5 years for a duration of 7 days at a dose of 10 mg once daily.

Vaccines: Immunoprophylaxis is also given for high risk individuals. The vaccines licensed in India are detailed in table3.

Infection Control Measures: Airborne isolation is necessary in order to contain infective droplets from patient surroundings. Airborne transmission based precautions are advocated for all Influenza virus infected patients. Use of N95 mask and hand hygiene by health care workers should be

ensured during patient care. Cough etiquette is mandatory to prevent spread of infection.[13]

Crimean Congo Hemorrhagic Fever (CCHF)

CCHF is caused by Nairovirus which is a single stranded RNA virus causing hemorrhagic fever. The virus is transmitted by bite of Hyalomma tick, contact with blood and body fluids of infected humans and animals. Following its discovery in 1944, various outbreaks have occurred, the last one being in 2012 at Pakistan. The case fatality rate of this infection ranges from 9-50%.[14] It has an incubation period ranging from3-6 days.

Mode of Transmission

Primary Human Infections: 80-90% humans are infected through the bite or direct contact with blood of infected ticks. They can acquire infection also through direct contact with blood/tissues of infected wild animals and livestock.

Secondary Human Infections: Human to human transmission occurs through direct contact with an infected person`s blood, secretions, organs or other body fluids. High risk of transmission occurs while providing direct patient care or handling dead bodies during funerals or autopsy.

Signs and symptoms of CCHF: Common symptoms of CCHF are high fever, chills, headache, joint pain, myalgia. Pulmonary manifestations of CCHF include acute respiratory distress syndrome at early phase of disease. Hemorrhagic phase of the disease presents with hemoptysis, pulmonary hemorrhage and hemothorax.[15] Complications manifest as disseminated intravascular coagulation, hypovolemic, multi organ failure.

Diagnosis: Laboratory diagnosis is a challenge since all clinical samples are highly infectious and a Biosafety level 4 (BSL-4) is mandatory. Therefore, samples should be transported and tested in laboratories with such facilities. Definitive or confirmatory diagnosis requires one of the following[16]:

1. Real time reverse transcriptase for detection of viral RNA done during the pre-hemorrhagic period and the hemorrhagic period (first 10 days after onset of symptoms).
2. IgM antibody detection by ELISA (7 days – 4 months)
3. IgG antibody detection by ELISA (7 days – 5 years)
4. Antigen detection – Immunohistochemical staining of infected tissues
5. Viral isolation by cell culture on Vero cell lines, LLC-MK2, CER and BHK21 cells.
6. Intracerebral inoculation of suckling mice
7. Serum neutralization test
8. Other methods (Solid phase radioimmunoassay, immunofluorescence, complement fixation, hemagglutination)

Treatment and Prevention of CCHF: As of today there are no FDA US approved drugs for treatment of CCHF. However, use of Ribavirin has shown benefits from few studies and is also recommended as a post exposure prophylaxis drug.[17]Handling outbreaks by following standard and contact precautions are necessary due to its lethal nature. Suspicion of CCHF on seeing cases with overlapping presentations and initiation of immediate control measures are the roles prudent health care workers and clinicians.

Coronaviruses

These group of viruses are usually viruses of public health importance because of their rapid dissemination through contact and respiratory droplets. Apart from this they cause health care associated outbreaks and have high case fatality rates. Coronaviruses are single stranded enveloped RNA viruses belonging to family Coronaviridae.

Table 1 Emerging viruses, year of outbreaks, place of discovery.[3,4]

Viruses	Year of origin and outbreaks	Place of discovery
Avian Influenza (H5N1)	1997, 2003, 2004 - 2013	China, Hong Kong
Avian Influenza (H7N9)	2013	China
Avian Influenza (H5N9)	2016	France
Avian Influenza (H9N2)	1994-2013	China
Swine flu - Influenza A (H1N1)	1918 (Spanish flu), 2009	USA, Hungary, China
Swine flu - Influenza A (H1N2)	2018	Asia, Europe
Swine flu - Influenza A (H2N2)	1957 (Asian flu)	Asia
Swine flu - Influenza A (H3N2)	1968 (Hong Kong flu)	Asia
Crimean-Congo haemorrhagic fever (CCHF)	1944, 1956, 1969, 2011, 2012	Crimea, Congo
SARS-CoV (Severe Acute Respiratory Syndrome – Coronavirus)	2002, 2003	Guangdong province of southern China
MERS-CoV (Middle East Respiratory Syndrome – Coronavirus)	2012, 2013	Saudi Arabia, Qatar
Human Coronavirus NL63, HKU1	2004	Europe, Japan, China, Australia, and North America
Ebola	1976, 1989, 2008, 2012, 2014, 2018	Ebola river, Congo, Africa
Hanta virus	1993	United States of America
Nipah virus	1999, 2001, 2007, 2018	Nipah village, Malaysia
Rift valley fever virus (Phlebovirus)	1931	Kenya
Human Bocavirus	2005, 2010	Sweden
Human Metapneumovirus	2001	Netherlands
Dengue	1950s	Philippines, Thailand

Table 2 Diagnostic methods for detection of Influenza virus

Method	Description
Cell culture	Cell lines : Madin – Darby canine kidney (MDCK) cells Detection of cytopathiceffects : Immunofluorescence, hemagglutination, hemagglutination inhibition.
Embryonated egg culture	Amniotic cavity is selected since it supports growth of Influenza A,B,C viruses. Allantoic cavity supports the growth of only Influenza A virus. Detection of growth :Hemadsorption, hemagglutination.
Antigen detection	Immunofluorescence antibody staining of virus infected cells, rapid immunochromatography.
Antibody detection	Hemagglutination, hemagglutination inhibition, neutralization assay.
Molecular diagnosis	BSL-2 containment and BSL-3 practices are required for molecular labs processing samples. Methods : Conventional and real time reverse-transcriptase PCR (RT-PCR), Restriction Fragment Length Polymorphism (RFLP), probe hybridization, genetic sequence analysis.

Table 3 Details of Influenza vaccines in India

Name of vaccine	Type of vaccine	Route of administration	Dose	Viral strains targeted
Agrippal	Inactivated surface antigen (trivalent)	Subcutaneous injection	0.5 ml	H1N1 pdm09 (A), H3N2 2016 (A), Mary Land 2016 wild type (B)
Fluarix	Inactivated quadrivalent vaccine	Subcutaneous injection	0.5 ml	H1N1 pdm09 (A), H3N2 (A), Brisbane 2013 wild type (B), Phuket 2008 wild type (B)
Influgen	Inactivated (fixed virus)	Intramuscular / subcutaneous	0.5 ml	Influenza A&B 30mcg, H1N1 15mcg
Influvac	Inactivated surface antigen (trivalent)	Intramuscular / subcutaneous	0.5 ml	H1N1 pdm09 (A), H3N2 2016 (A), Phuket 2016 wild type (B)
Nasovac	Inactivated freeze dried	Inhalation	0.5 ml	Reassortant of Pandemic H1N1 2009 (A) - California strain
Vaxigrip	Inactivated trivalent Types A & B	Intramuscular	0.5 ml	H1N1 pdm09 (A), Texas H3N2 2012 (A), 2012 Massachusetts (B)

Table 4 Management of Coronavirus infection

Early supportive therapy and monitoring	1.Patients with signs of respiratory distress, hypoxemia or shock : Give oxygen therapy. 2.Patients with respiratory distress and no evidence of shock : Use conservative fluid management. 3.Closely monitor for signs of deterioration to respiratory failure and sepsis. 4.Manage co morbid conditions of patient, if present. 5.Avoid high dose steroids and other adjunctive therapies.
Management of severe respiratory distress, ARDS and hypoxemia	1.Early recognition of hypoxemic respiratory failure due to failing standard oxygen therapy. 2.Selected cases of non-hypercapnic hypoxemic respiratory failure : Use high-flow oxygen (up to 50 L/min). 3.Early institution of mechanical ventilation if hypoxemia persists despite high flow oxygen therapy. 4.Rapid sequence induction for endotracheal intubation. 5.Initiate lung protective ventilation strategy for ARDS after intubation. 6.Allow permissive hypercapnea to reach LPV strategy. 7.Use adequate PEEP to reach target SpO_2. 8.If tidal volume is not controlled, consider deep-sedation targets. 9.Consider early adjunctive therapeutics in moderate-severe ARDS with failure to reach LPV targets. 10.Prone position is recommended, administer neuromuscular blockade for initial 48 hours, use higher PEEP levels, use a conservative fluid management strategy.
Management of septic shock	1.Look for hypotension which persists after adequate fluid challenge indicative of sepsis-induced shock. Early resuscitation initiation. 2.Intravenous crystalloids : Early and rapid infusion is suggested. 3.Administer vasopressors if shock persists despite fluid resuscitation. 4.Consider inotrope (Dobutamine) if signs of poor perfusion and cardiac dysfunction continues. 5.Consider hydrocortisone or prednisolone in persistent shock. Taper when shock resolves.
Prevention of complications	1.Weaning protocols to reduce days of invasive mechanical ventilation. 2.VAP bundle should be used to reduce incidence of ventilator-associated pneumonia. 3.Heparin prophylaxis to reduce incidence of venous thromboembolism. 4.Reduce incidence of central line related blood stream infection (Bundle care and other measures). 5.Turn patient every two hours to reduce incidence of pressure ulcers. 6.Give early enteral nutrition, administer H2 blockers or proton pump inhibitors to reduce incidence of stress ulcers/gastric bleeding. 7.Reduce incidence of ICU-related weakness – Early mobility.

Table 5 Diagnostic Methods for Ebola virus disease[36]

Direct detection of virus	Description
1.Indirect immunofluorescence	Screening assay on gamma-inactivated, fixed cells infected with EBOV or expressing recombinant filovirus proteins → Ag : rNP
2.Electron microscopy	Due to relatively high viremia levels in humans
3.Virus isolation	Vero or Vero E6 cells, Guinea pigs, do not grow well in tissue culture
4.Polymerase chain reaction	Target genes : NP, L
5.Immunohistochemistry (IHC)	Done on fixed material and paraffin-embedded tissues and on impression smears of tissues
Antigen detection	ELISA (Antigen detected – Viral Glycoprotein) Indirect Immunofluorescence (IFA)
Antibody detection	ELISA (Antibodies to recombinant nucleoprotein – r NP)

Table 6 Features of miscellaneous emerging viruses with respiratory involvement

Virus	Mode of transmission	Respiratory manifestations	Laboratory diagnosis	Treatment and prevention
Rift valley fever virus	Exposure to blood and tissue of viremic livestock, inhaling aerosols containing virus.	Case fatality : 50% Influenza like syndrome, Hemorrhagic syndrome.	Cell culture, antigen and antibody detection by ELISA, HAI, PRN, PCR.	Supportive care. Live attenuated vaccine MP-12, live attenuated clone 13 vaccine.
Bocavirus	Inhalation of contaminated respiratory droplets.	Croup, pneumonia, bronchiolitis, upper respiratory tract infection.	PCR. No definite diagnostic method available.	Supportive management. No vaccines available.
Metapneumovirus	Secretions through coughing, sneezing.	Rhinitis, laryngitis, bronchiolitis.	IFA, ELISA for viral antigen, PCR.	Supportive management. No vaccines available.
Dengue virus (Flavivirus)	Bite of mosquito *Aedesaegypti*	Cough, hemoptysis, dyspnea, pleural effusion, ARDS, pulmonary edema, pneumonia, pulmonary hemorrhage.	NS1 antigen, IgM, IgG antibodies by ELISA, PCR.	Supportive therapy, iv fluids

Severe Acute Respiratory Syndrome – Coronavirus (SARS-CoV)

Termed as the first emerging infectious disease of the 21`st century, SARS was discovered in 2002 in the Guangdong province of China. Beginning there, this virus spread to various parts of Asia as well as neighboring continents claiming the lives of hundreds of contacts and health care workers.[7,18]

The 2002-2003 epidemic halted due to highly coordinated and global public health response by the World Health Organization. A suspected case of SARS is defined as "A person with documented fever (Temperature >38°C), contact with a person having suspected SARS infection or travel to a geographic location where transmission of illness is documented, lower respiratory tract infection". A probable case is defined as "A suspected case with radiological features of pneumonia, ARDS, unexplained respiratory illness resulting in death and pathology autopsy ARDS seen during autopsy without an identifiable cause".[19]

Risk Factors: People at risk of infection are elderly, children and individuals with an underlying medical illness. Seventy percent of patients with SARS develop complications and serious illness requiring respiratory support. Elderly as well as those with underlying conditions are at higher risk of

secondary infection and mortality.[20]Tobacco smoking and co-infection with other respiratory viruses are the other documented risk factors for acquiring SARS-CoV.[21,22]Apart from this, health care workers treating and handling infected individuals are also at risk of acquiring infection.

Mode of Transmission: SARS CoVgets transmitted on close contact with infected individuals. Inhalation of coughed droplets containing infective viruses gain entry and establish themselves in the respiratory tract of host thereby causing infection.

Clinical Symptoms and Signs: Infected individuals present withacute onset of influenza-like illness with fever associated with rigors, headache, malaise, myalgia, diarrhea. In few cases especially elderly and immunocompromised, fever might not be the presenting symptom. Symptoms such as non-productive cough, breathlessness and diarrhea appear usually in first or second week of illness. In severe cases, there is rapid progression torespiratory distress requiring ventilator support and eventually death.[23]

Middle East Respiratory Syndrome– Coronavirus (MERS-CoV)

This new emergence of viral zoonosis posed a global threat in 2012 after claiming human lives in the Middle East.The epidemic was linked to transmission of Coronavirus form animals (dromedary camels) to humans due to close contact.Approximately 37% of infected individuals expired during the initial outbreak.[24]

Risk Factors: Humans at risk of acquiring infection are those coming in contact with infected animals namely dromedary camels which are abundant in Middle East countries like Saudi Arabia and the UAE. Animal exposures in household areas as well as farms, live animal markets, racetracks and slaughter houses are other sources of acquiring the virus. The virus appears to cause more severe disease in elderly, immunocompromised and those with chronic illness such as carcinoma, chronic lung or chronic kidney disease and diabetes.[25]

Mode of T

Ransmission: Animal to human transmission is linked to direct or indirect contact of humans with camels although the route of transmission is unclear. Humans acquire infection on close contact with infected individuals especially while providing unprotected care to them at health care facilities.[25]

Clinical Symptoms and Signs: The clinical presentation may range from asymptomatic illness to very severe disease. Typical presentation includes fever, cough and breathlessness. Other common presentation of MERS-CoV is pneumonia which may not always be present. Severe illness is characterized by acute pneumonia with fever, respiratory distress and failure requiring ventilator support. Extrapulmonary complications such as acute kidney injury, seizures, hepatic failure and gastrointestinal symptoms have been documented from severe cases. [26] Severe pneumonia, ARDS, sepsis and septic shock are end stage complications resulting in high mortality.

Diagnosis of Coronaviruses: The most common laboratory abnormalities noted among infected patients include lymphopenia, elevated levels of lactate dehydrogenase, aspartate aminotransferase and creatine kinase. Mild thrombocytopenia and mild leukopenia are less common.

Revised guidelines for diagnosis of MERS CoV was released by the World Health Organization in January 2018. It is mandatory to process all samples in a BSL-2 laboratory facility with a biosafety cabinet 2 or 3. Recommended samples for virus detection are nasopharyngeal swabs, oropharyngeal swabs, nasopharyngeal aspirates/wash, sputum, bronchoalveolar lavage, tracheal aspirates. Serum samples (paired serum) are collected for serological diagnosis in the first week as well as 3-4 weeks thereafter.

Nucleic acid Amplification (NAAT): Real-time Reverse-Transcription Polymerase Chain Reaction (rRT-PCR) is the most rapid method for detecting viral RNA.Reverse Transcription-Loop-mediated isothermal Amplification (RT-LAMP) and Reverse Transcription isothermal recombinase Polymerase Amplification (RT-RPA) are othe
1.r molecular methods used for diagnosis of Coronaviruses.[26]

Viral Culture: Virus culture is not recommended as a routine diagnostic procedure. Studies on viral properties and vaccine research studies can be performed by culturing Coronaviruses on Vero, LLC-MK2, Caco-2, and Huh-7 cell lines.[26,27]

Antigen Detection: Commonly used target protein for antigen detection is Nucleocapsid protein.

Antibody Detection: Antibodies in serum of infected individuals can be detected using immunofluorescence assay (IFA), neutralization, protein microarray, ELISA. Microneutralization test is the serological confirmatory test. IFA and ELISA are used as screening tests.

Treatment and Prevention of Coronaviruses: Like any other emerging virus, Coronaviruses do not have a specific treatment. The treatment strategies proposed by the WHO are as follows (Table 4)[28]:

Monoclonal antibodies against MERS-CoV (4C2, 2E6, 3B11, LCA60, Mersmab1,M336, m337, m338, D12, F11, G2, G4, MERS-4, MERS-27 ETC.) and few antivirals (Mycophenolic acid, lopinavir, HR1P, HR2P) can be used as adjunctive therapy.[29]

Prevention of spread of infection from one person to another can be achieved by following strict infection control measures such as standard precautions, droplet isolation, hand hygiene, cough etiquette etc. No licensed vaccines are available till date for immunoprophylaxis against Coronaviruses.

Ebola Virus

Discovered as a major cause of viral hemorrhagic fever in 1976 in Africa, Ebola has produced fatal outbreaks on and off ever since. Although not exclusively a respiratory virus, Ebola virus produces major pathological pulmonary complications. Almost all patients have respiratory involvement as respiratory droplets carrying viral particles form a major source of transmission apart from direct contact. Case fatality rate ranges from 30% to 90%.

Risk Factors: Consumption of bush meat or contact with secretions of infected animals (bats, non-human primates), close contact with secretions of infected humans (sweat, blood, faeces, vomit, saliva, genital secretions, urine, and breast milk) are major risk factors.[30,31]Travellers to affected areas,

laboratory workers, handlers of dead infected individuals are at risk of acquiring Ebola.

Mode of Transmission: Humans acquire infection by direct contact with secretions and body fluids of infected individuals and animals. Maximum transmission has been reported in health care facilities while treating patients.[32]

Clinical Features: Incubation period ranges between 1 – 9 days. Major respiratory manifestations of Ebola are cough, dyspnea, chest pain, pulmonary hemorrhage and respiratory failure. Interstitial pneumonia has been documented.[33]Pulmonary signs and symptoms appear due to active viral replication in alveolar macrophages, endothelial cells and monocytes as the virus has a wide cell tropism.[34]

Prodrome (early symptoms – 8 to 12 days): Fever, chills, headache, fatigue, vomiting, diarrhea, myalgia, sore throat, rash, anorexia, nausea, abdominal pain.

Fatal cases (worsening of symptoms – 2 weeks after exposure): Hemorrhagic manifestations, anuria, tachypnea, coma, multi organ failure, shock.

Common clinical signs of Ebola infection are hyperthermia, tachypnea, tachycardia or bradycardia, hypotension.[35]In fatal cases, death usually occurs 1-2 weeks after development of symptoms.

Laboratory Diagnosis: A confirmed case of Ebola is classified based on a positive diagnostic test from the patient (IgM ELISA/antigen/RT-PCR). Therefore laboratory diagnosis plays a pivotal role in case definition as well as epidemiological purpose. A biosafety containment level 4 is mandatory requirement for processing suspected clinical samples.

Antemortem Diagnosis: Serum samples are used for diagnosis at this stage.

Postmortem Diagnosis: Tissue samples from liver, spleen, bone marrow, kidney, lung, brain are used for postmortem diagnosis.

Sample storage: Samples for testing can be stored at room temperature for 24 hours. For the next one week, samples should be stored at 0-5°C. If further storage is required, store samples at -20 to -70°C after one week of collection. Freeze-thaw cycles should be avoided.

Sample containers should be wiped on the exterior with 1% sodium hypochlorite or 5% lysol.All samples are packed as per WHO guidelines in three containers (primary, secondary, tertiary).

Constitutional laboratory findings in Ebola are leukopenia, lymphopenia, thrombocytopenia, elevated serum transaminase levels, hyperproteinemia and albuminuria, prolonged prothrombin, partial thromboplastin time. However, viral detection is the gold standard for diagnosis of Ebola. Various viral diagnostic methods are briefed in table 5.

Treatment of Ebola: There is no specific treatment for Ebola. Monoclonal antibodies were tested for their efficacy against Ebola. ZMapp, a cocktail (combination of monoclonal antibodies) proved to show neutralizing effects on Ebola virus. ZMapp binds to the antigenic epitope on the envelop glycoprotein (GP) thereby neutralizing the virus and arresting viral replication. Other chimeric monoclonal antibodies with proven viral binding are ZMAb and MB-003.[37] Antiviral, Brincidofovirhas shown in vitro action against Ebola. A new interference agent, TKM-Ebola (RNA lipid nanoparticle product) has shown to improve survival in adults who were given intravenous infusion in clinical trials.[38]Supportive care should include intensive care unit with ventilators for patients developing respiratory distress and hypovolemic shock due to hemorrhage.

Prevention of Ebola: Strict infection control practices are advocated to prevent human – human transmission in health care facilities. Some of the recommended practices are:

1. Isolate the patient.
2. Follow standard precautions.
3. Use adequate Personal Protective Equipments.
4. Avoid procedures which potentially generate aerosols.
5. Visitors should be restricted.
6. Proper disposal of biomedical waste.
7. Environmental infection control practices should be adhered.
8. Proper and careful disposal of dead bodies in leak proof impermeable plastic bags is mandatory. Funeral rituals should be avoided.
9. Spill of blood and body fluids should be disinfected appropriately.

Two Promising Candidate Vaccines Under trial are

cAd3-ZEBOV→ uses a chimpanzee-derived adenovirus vector with an Ebola virus gene inserted.
rVSV-ZEBOV→ uses an attenuated or weakened vesicular stomatitis virus, a pathogen found in livestock; one of its genes has been replaced by an Ebola virus gene.

Hendra and Nipah (Henipa) Viruses

Hendra virus (HeV) and Nipah virus (NiV) are termed as emerging zoonotic viruses. Both these viruses cause severe fatal respiratory distress, respiratory failure and encephalitis in humans and animals. Phylogenetic similarities resulted in reclassification of these viruses as Henipa virus. Epidemiological niches of these viruses are concentrated in parts of the world where the animal reservoir fruit bats (*Pteropusgiganteus*) are present.

Mode of Transmission: Transmission occurs either directly from an infected human to a normal individual or from infected animals to humans.[39] Infected pigs can transmit the virus to humans working in close proximity in pig farms and hence act as intermediate hosts. Hendra virus infects horses and humans handling infected horses. Health care workers treating infected patients are at high risk of acquiring infection. Case fatality rates ranging from 40-75% have been reported from various outbreaks.

Direct Transmission: Occurs from pigs to humans, humans to humans or bats to humans.

Indirect Transmission: Occurs due to consumption of date sap contaminated with the urine, saliva or feces of fruit bats.

Clinical Features: Henipa viruses may present as Acute Encephalitis Syndrome (AES) or acute lower respiratory infection (ALRI). Intensity of respiratory manifestations of these viruses vary depending on the type of strain causing outbreak. The major target cells for Henipa viruses are endothelial cells present in the blood vessels, viral receptors present in lungs, nervous system, spleen, kidneys. Although

the exact route of transmission is unknown, nasal passages are first targets of viral replication.[40]

Nipah virus infection starts in the trachea and then progresses down to the bronchial epithelium and alveoli producing hemorrhagic pneumonia. Contrasting feature is noted with Hendra virus where the smaller airways are primarily affected and retrograde progression is noted with involvement of trachea and bronchi.[40,41]Clinical features of Henipa virus includes influenza like illness which can progress to pneumonia and respiratory distress syndrome.[42]

Laboratory Diagnosis: Maximum containment (Biosafety level 4) laboratory is required for processing samples from suspected Nipah cases. Main stay of diagnosis is detection of IgM antibodies, PT-PCR and viral isolation. Samples used for testing are blood, CSF , throat swabs and urine.

Treatment: Symptomatic and supportive care should be given after cohorting/isolating all suspected cases. Supportive care constitutes :

1. Intensive care for respiratory support and hemodynamic management.
2. Fluid maintenance and electrolyte balance.
3. Nutrition: Nasogastric tube feeds / Total parenteral nutrition.
4. Oropharyngeal suctioningusing a closed circuit.
5. Inhalational oxygen using disposable cannulae.
6. Bronchodilators.

Studies using Ribavirin as specific therapy has shown better survival compared to patients not treated with Ribavirin. Monoclonal antibodies have been used as post exposure therapy for neutralization of viruses.[43,44]
Strict infection control measures should be followed similar to that described for other highly contagious viral pathogens. Reporting of all suspected as well as confirmed cases to respective health surveillance departments at state and national levels is mandatory to control outbreaks and prevent further spread of infection.

Hantavirus

Hantavirus is a rodent borne hemorrhagic fever producing virus common in Americas. It causes Hemorrhagic fever with renal syndrome (Case fatality rate: 5-15%) and Hantavirus pulmonary syndrome (Case fatality rate: 40-50%) also referred to as Hantavirus cardiopulmonary syndrome (HCPS).Species of Hantavirus are: Hantaan virus, Pumala virus, Seoul virus, Sin Nombre virus and Dobrava-belgrade virus.[2]Evidence of Hantaviral antibodies in India have been documented from Vellore in 1964, Chennai and Cochin in 1998-99, Mumbai in 2005.[45-48]

Mode of Transmission: Reservoirs of this virus are striped field mice (*Apodemusagrarius)* and deer mice (*Peromyscusmaniculatus*). Humans acquire infection on inhalation of infective aerosols from rodent feces, urine or salivacontaining the virus and through rodent bites.[49,50]Infections are common during rainy season when these rodents get dispersed from forestsinto human habitats seeking food and shelter. Human to human transmission is still not documented.
Clinical features: Infected individuals present with early symptoms of fever with chills, headache, myalgia involving large muscle groups, nausea, vomiting, dizziness. Late symptoms appear 4 – 10 days later and include non-productive cough,breathlessness, tightness of chest.An average of 38% individuals have rapid worsening of acute respiratory distress leading to fatal outcome.

Laboratory Diagnosis: Serological diagnosis using Immunofluorescence, ELISA, Plaque reduction neutralization (PRN), Haemagglutination inhibition can be done. Detection of viral RNA is done in serum by RT-PCR, immunohistochemistry is done for detection of viral antigen in tissues.[51]

Treatment and Prevention: Ribavirin has shown to decrease fatality due to Hantavirus pulmonary syndrome. Interferon α usage has no effect on fatality but has shown to have a minimal effect on the clinical course of disease. A compound named tragacanthin polysaccharide has antiviral property and has been suggested as a potential therapeutic agent against Hantavirus.[52]There are no WHO-approved vaccines for use, however locally developed vaccines are in use in Korea, China. Supportive management with respiratory support and oxygen therapy help to alleviate respiratory distress.

Other Respiratory Viral Pathogens

The other emerging viruses having respiratory involvement are: Rift valley fever virus, Human Bocavirus, Human Metapneumovirus and Dengue virus. The features of these viruses are collectively explained in table 6.

Apart from these viruses, Zika virus is another emerging virus which has been isolated from nasopharyngeal swabs of few infected individuals. Few infected individuals have reported upper respiratory tract involvement and sore throat. Lung tissue from a fatal case also showed presence of Zika virus.[53]
Maediis a slowly progressing disease in sheep with lung involvement resulting in interstitial pneumonia. The natural transmission of maedi is mainly by the respiratory route. It produces lymphoid hyperplasia in lungs.[54]It is still unclear if infected sheep can transmit this slow virus to humans coming in contact with them.

CONCLUSION

Many factors such as frequent international travel and trade, dispersion of animals species, human recreational activities, tending exotic pets, import and export of animal products, bioterrorism etc. have all lead to emergence and re-emergence of virus escausing respiratory infection. Respiratory system is most vulnerable due to the easily transmissible nature and rapid propagation of emerging viruses through inhalation. Collative understanding of emerging respiratory viruses is therefore essential to handle outbreaks as well as unusual occurrences in any given point of time.

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