DIFFERENCES IN THE EPIDEMIOLOGICAL OF H5N1, COVID-19 AND OTHER GLOBAL ZOONOSIS FLU

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ABSTRAC

Human avian influenza has caused serious outbreaks in several countries, especially in Asia, one of which is Indonesia. Human avian influenza has become an important public health problem because of the high mortality rates and because of the possibility of causing a global pandemic. The source of the virus is thought to come from bird migration and transport of infected birds. Laboratory tests can be done by examining leukocytes, platelets in suspected cases. Clinically suspicious of AI testing can be done simultaneously, which is taking blood for serology, throat swabs, nasopharynx, and oropharynx for RT-PCR examination and viral culture gold test as confirmation. Until now it is known that there have been five zoonotic flu diseases that cause a global pandemic and have taken many casualties in the world including SARS, MERS, H1N1, H5N1, and new diseases namely COVID-19. The method to be used for this review is literature study. The data obtained were compiled, analyzed, and concluded in order to get conclusions about the literature study. The five zoonotic flu diseases have differences from one another. So the classification of differences between H5N1 with each of the zoonotic flu diseases above needs to be done.

Keywords: *Avian influenza (AI) H5N1 virus, Covid19, Epidemiology, Global pandemic, Zoonotic flu*

1. INTRODUCTION

Human avian influenza is an infection that occurs in humans caused by the influenza A virus subtype H5N1. Avian influenza was discovered to attack in Italy about 100 years ago. This outbreak virus struck humans in Hong Kong in 1997 with 18 victims and six of them dead. Avian influenza (H5N1) or highly pathogenic avian influenza (HPAI) has caused serious outbreaks in several countries, especially in Asia. Since May 2005 the number of confirmed cases of avian influenza A (H5N1) has expanded to various countries in the world. Human avian influenza (H5N1) has become an important public health problem because it has a high mortality rate and

likely to cause an influenza pandemic.[1]

Avian Influenza (AI) is a contagious avian disease caused by influenza type A viruses from the family of Orthomyxoviridae. This virus most commonly affects birds (for example domestic chickens, turkeys, ducks, quails, and geese) as well as various wild birds. Some bird flu viruses are also known to attack mammals, including humans.[2]

Based on data from the Ministry of Research and Development of the Ministry of Health (2005), avian influenza transmitted by Avian Influenza type H5N1 viruses in poultry has been confirmed to have occurred in the Republic of Korea, Vietnam, Japan, Thailand, Komboja, Taiwan, Laos, China, Indonesia, and Pakistan. The source of the virus is thought to come from bird migration and transport of infected birds.[3]

Until now the AI pandemics still occur in both developing and developed countries, the possibility of transmission from the movement of birds from endemic to non-endemic countries. Although AI disease attacks poultry, or other livestock, but can transmit to humans. Transmitted between humans, can not be proven. The laboratory tests can be carried out by examining leukocytes, platelets carried out in suspected cases. A suspicious clinical examination of AI can be done simultaneously, namely taking blood for serology, throat swabs, nasopharynx, and oropharynx for RT-PCR examination as well for viral culture gold test as confirmation. Weaknesses in laboratory examinations, not all referral laboratories can perform RT-PCR examinations.[4]

The Ministry of Health of the Republic of Indonesia said that as of 30 December 2005, 142 cases of poultry influenza infections in humans had been reported from various regions. At that time human transmission was still limited in Cambodia, Indonesia, Thailand, with epicenter in Vietnam (65.5% of all cases), 72 people (50.7%) had died. This number has now increased again, especially with the widespread and increasing deaths in Indonesia. Also from several other countries (Turkey, Iraq), there have been reports of cases of this avian influenza in humans. Cumulative cases of H5N1 since 2014-2018 were 860 cases with 454 deaths (CFR 53%). Based on data from the Indonesian Ministry of Health (2019), in 2018 there were no H5N1 cases reported yet. Cases in Indonesia from 2005 to 27 October 2018 were 200 cases with 168 deaths (CFR 84%).[5]

Until now it has been known that there have been five zoonotic flu diseases that cause a global pandemic and have taken many casualties in the world including SARS, MERS, H1N1, H5N1, and new diseases namely COVID-19. The five zoonotic flu diseases have differences from one another.

2. METHODS

The data collection method is literature study. The method to be used for this review is literature study. The data obtained were compiled, analyzed, and concluded in order to get conclusions about the literature study. Research with literature studies is a study whose preparation is the same as other research, but the sources and methods of data collection are by taking data from libraries, reading, taking notes, and processing research materials. Research with literature studies is also a study and can be categorized as a scientific work because data collection is carried out with a strategy in the form of a research methodology.

3. RESULT AND DISCUSSION

EPIDEMIOLOGY

1. Agent

The virus that causes bird flu is classified as family orthomyxoviridae. Viruses consist of 3 different antigenic types, namely A, B, and C. Influenza A viruses can be found in poultry, humans, pigs, horses, and sometimes other mammals, such as mink, seals, and whales. However, natural horpes are wild birds. In contrast, influenza B and C viruses are only found in humans (shown in **fig.1**). Avian influenza also called avian influenza, is caused by influenza A virus. This virus is an RNA virus and has haemagglutinin (HA) and neuraminidase (NA) activity. The division of virus subtypes is based on the surface of the antigen, the surface of the hemagglutinin, and the neuraminidase they have.[6]

2. Clinical Symptoms

According to Vascellari (2007), the symptoms of bird flu are highly variable and depend on the infected bird species. The incubation period of this virus for poultry ranges from a few hours to 3 days, sometimes 7 days depending on the dose of the virus, the route of contact, and the species of poultry attacked. Whereas in humans 1-3 days, the infection period is 1 day before until 3-5

days after symptoms appear. In children for up to 21 days. Avian influenza in poultry can be found in two forms, namely mild form an acute form (highly pathogenic avian influenza, HPAI.[7]

The symptoms of ducks/poultry attacked by bird flu include such as neck twisted, convulsions, difficulty standing, lack of appetite, vaginal discharge, for laying ducks egg production suddenly decreases (weakness, flaccid eggshell), and widespread bleeding or spots are often found in the trachea mucosa, proventriculus, intestine, fat layer, chest muscles, and legs.[7]

According to Damayanti (2004), human symptoms of bird flu that is, the majority of sufferers of AI (H5N1) symptoms are the same as another influenza early fever over 38°C and lower respiratory tract symptoms. Diarrhea, vomiting, abdominal pain, chest pain (pleuritic), and bleeding from the nose and gums. The resulting sputum varies sometimes with blood, respiratory distress, tachypnea, and cracked inspiration. Diffuse progressive respiratory failure, bilateral, infiltration, and display of acute respiratory symptoms (ARDS = Acute Respiratory Distress Syndrome).[8]

Failure of many organs of the kidney, heart dysfunction including dilation and supraventricular arrhythmias. Other complications associated with ventilation are pneumonia, pulmonary bleeding, pneumothorax, pancytopenia, symptoms of Reye, and sepsis without bacteremia. Early-onset of a sudden and rapidly worsening disease, high fever, muscle aches, and dry cough are often found in AI infections (H5N1). Differential diagnoses of AI (H5N1) include respiratory syncytial virus (RSV), adenovirus, parainfluenzavirus, rhinovirus, Mycoplasma pneumonia, Chlamydia.[8]

3. Chain Of Infection

According to Ong (2008), the influenza A / H5N1 virus is very virulent and contagious, at first, transmission only occurred between wild birds and then spread among poultry through livestock, equipment, transportation equipment, food, pens, and clothing. After an outbreak of avian influenza infection in poultry, this virus can spread from birds to humans. This influenza A virus can cause a pandemic because it is easily mutated, either in the form of antigenic drift or antigenic shift to form new variants that are more pathogenic.[9]

WHO (2008) states that the exact time when exposure is difficult is determined because in many cases the exposure is repeated many times, but the estimated incubation period for H5N1 virus infection in humans after exposure to sick poultry is generally between 2-7 days, and in one cluster case it is estimated reach 8-9 days.[10]

Transmission can also occur indirectly, for example through air polluted by material/dust containing influenza viruses (aerosols); food/beverage, livestock equipment/supplies, cages, chicken cages, clothing, vehicles, egg trays, birds; mammals and insects that contain or are contaminated with influenza viruses. In connection with the mode of transmission, the influenza virus can be spread easily to various regions by people or equipment/equipment and vehicles used to market poultry products.[8]

4. Natural History Of Disease

A. Prepathogenesis

According to Ririh (2006), the susceptible phase (pre-pathogenesis) is the stage of the etiological process, in which the first causative factor meets the host for the first time (Host). This first causative factor has not yet caused the illness but has begun to lay the foundations for future disease development. This first causative factor is also called a risk factor because its presence leaves the possibility of disease occurring before the irreversibility phase.

The vulnerable stage in bird flu is people who are in endemic areas. At this stage, the spread and transmission of the virus occur, but the process of spreading is not yet fully understood. Ducks and geese are carriers of influenza A subtypes H5 and H7. This wild waterfowl also becomes a natural reservoir for all influenza viruses. It is estimated that the spread of the bird flu virus was due to migration from these wild birds.[11]

B. Pathogenesis

This stage includes 4 sub-stages, namely :

a) Incubation Stage

On Poultry: 1 week

In Humans: 1-3 days, The infection period is 1 day before until 3-5 days after symptoms appear. In children for up to 21 days.

b) Early Disease Stage

This stage is through the appearance of symptoms of a disease that seems mild. This stage has started to become a health problem, in the form of diarrhea, vomiting, abdominal pain, chest pain, hypotension, and bleeding from the nose and gums can also occur.[11]

c) Advanced Disease Stage

At this stage shortness of breath begins to occur after the next 1 week. Clinical symptoms can worsen rapidly which is usually characterized by severe pneumonia, dyspnea, tachypnea, abnormal radiographic features such as diffuse, multifocal, patchy infiltrates; interstitial infiltrates; and segmental or lobular abnormalities. Death and complications are usually caused by respiratory failure, acute respiratory distress syndrome (ARDS), ventilator-associated pneumonia, pulmonary hemorrhage, pneumothorax, pancytopenia, Reye's syndrome, sepsis syndrome, and bacteremia.[12]

C. Pascapathogenesis

In this final stage, most sufferers end in death. Mortality rates indicate that the H5N1 virus has a high virulence rate. This is because the more freely the avian influenza virus causes severe pain which can no longer be saved.[12]

5. Distribution Of Person, Place and Time

A. Person

Judarwanto's research (2005) states that out of 86 confirmation cases, 56% were male and 44% were female. The distribution of cases according to the age group 0-5 years was 11.24%; 6-15 years as much as 28.09%; 15-45 years 59.55%, and >45 years 1.12%. Bird flu sufferers are more prevalent in males and afflict productive age, this is possible because of exposure to higher risk factors in males and productive ages.[13]

At present the second largest number of cases of bird flu in humans in Indonesia after Vietnam, with the highest mortality rate in the world. Compared to other countries that are also infected with avian influenza / H5N1, bird flu in Indonesia continues to grow and tends to increase from year to year. According to reports from the CDC that cases of Avian Influenza are more common in children and young adults, due to a higher risk of exposure. The proportion of cases previously exposed to several risk factors was 56.2%. Cases in infants occur due to an immune system that is not yet strong.[14]

Exposure to the H5N1 virus which may originate directly from poultry, which suffers from Avian Influenza (100%). This shows that toddlers are a high-risk group that needs to be maintained so as not to contact with birds and poultry. The case fertility rate in infants reaches 100%, followed by adults (87.5%) and school-age children (40%). The highest mortality rate of H5N1 infection occurred in infants (89%). The difference in mortality is caused by the difference in response rate that is carried out. Toddler mortality is high due to slow case management (> 2 days).[13]

B. Place

According to Judarwanto (2005), if an increase in cases in animals occurs, the risk of transmission to humans will also be even greater. In Indonesia, up to February 2006, cases of confirmed Avian Influenza have occurred in the provinces of Lampung, DKI Jakarta, West Java, Banten, and Central Java. The five provinces had previously experienced cases of Avian Influenza in poultry or other animals. The northern coastline (Pantura), especially Indramayu Regency, has airspace that every season is a traffic lane for millions of birds, including areas infected with the H5N1 virus. In the course of migration, birds from Australia or Europe that travel thousands of kilometers make the Rakit islands a resting place or transit. North Rakit Island, Gosong, and South Rakit or Biawak Island became a haven for millions of birds for 2-2.5 months to reproduce, mate, and even hatch their eggs.[13]

According to WHO (2006), in addition to weather events in animals are also affected by the migration of wild birds. The H5N1 virus with high pathogenicity (HPAI) can last a long time in environments with low air temperatures.[15]

C. Time

The Indonesian Ministry of Health (2006) states that in Indonesia the first case of Avian Influenza in humans and which ended in death occurred in July 2005 (shown in **fig. 2**). The case was shocking because it was experienced by people who did not work on the farm and whose homes were far from the farm location. Entering the rainy season, in September 2005, there was an increase in cases six times the cases in July 2005. After that, until February 2006 there were always reported new cases with fluctuating numbers. The weather when Avian Influenza was endemic in the September 2005 February 2006 period was the same as the weather when an outbreak occurred in animals in 2004, namely the rainy season.[16]

The relatively lower ambient temperature will make the virus last longer because it can survive in water at 22°C for four days. The nature of this virus can theoretically transmit to humans through the nose. The increase in winter cases is cause habit of staying indoors and the habit of bringing their livestock into the house. This causes more frequent contact, so the risk of transmission between animals or animals to humans becomes greater.[17]

6. Risk Factors

A. Knowledge

Knowledge is a very important domain for the formation of a person's presence and activities, therefore, community knowledge about the spread of bird flu is very important to see the extent of their knowledge about the causes, ways of transmission and prevention of bird flu to avoid the possibility of contracting bird flu.[18]

B. Cage Environment and Enclosure Personnel

Cage hygiene and personnel are part of biosecurity and are a potential aspect that influences the possibility of disease agents entering the farm. The spread of the bird flu virus between cages can be reduced by always maintaining the cleanliness of the cage and its equipment, especially if you always use the right disinfectant. Movement of people such as breeders, veterinarians, and guests on farms is one of the factors spreading bird flu virus between cages. According to Marangon and Capua (2005), analyzes conducted on cases of HPAI outbreaks in Italy during 1999/2000 showed that 9.4% of infections were indirectly due to exchanges of employees, equipment, and others.[19]

C. Factor Cage Break Time

The cage break time factor is very effective in reducing existing microbial populations. Microbes cannot last long in the environment, because for breeding they require a host (host). Farmers rest their cages for a long time if there are special reasons such as difficulty in getting seeds or when prices are high in the market. Even though the cage break is very effective in reducing the existing microbial population.[19]

D. Factor Distance Between Enclosures

The factor of the distance between cages on farms is important because the closer distance between cages will also increase the risk of contracting the disease if the nearest neighbor's farm is affected by the disease. A study in Italy showed that 26.2% of the incidence of bird flu was found in the environment within a radius of one kilometer around attacked farms. Poultry in a radius of 5-6 kilometers from a positive location of bird flu must continue to watch out for. While the IEC in a workshop in Hanoi stated that the bird flu virus is transmitted by birds or wild animals within a radius of 10 km from a positive location of bird flu, so radius it is considered a contagious zone that must be wary of.[20]

E. Maintenance System

The maintenance system factor is not one of age is one of the potential aspects that influence the possibility of avian influenza spread in livestock. One of the steps to prevent the spread of avian influenza virus between cages is by applying strict biosecurity, an all-in all-out maintenance system, always maintaining the cleanliness of the cage and the cage officers along with their equipment, and using appropriate disinfectants.[18]

7. Preventions

The avian influenza mortality rate is still high, so various prevention efforts are needed so that the disease does not occur. Some efforts can done to prevent avian influenza, including 5 levels of prevention, namely:

A. Primordial Prevention

No vaccine can prevent bird flu, it was difficult to handling if it has been infected by humans. Therefore the prevention of bird flu or the H5N1 virus is very important in the following way; training yourself and maintaining healthy food, washing hands with soap and dropping water after contact with poultry and other poultry products, also before preparing food and before eating, buy healthy poultry, do not eat raw blood, meat or eggs undercooked poultry, do not slaughter sick birds, do not eat dead or sick birds, avoid contact with infected sources, do not allow children to play near cages, do not allow birds to roam around the house, use masks or gloves when in contact or slaughter birds, bury poultry waste (feathers, viscera, and blood), bathing and changing clothes and clothes that are worn with contact with poultry washed with soap if you have a high fever, chest pain, difficulty breathing headaches and muscle aches ache after contact with poultry immediately go to the hospital to get the right treatment by a doctor.[11]

B. Primary Prevention

Primary prevention is prevention carried out on people who are at risk of contracting bird flu, can be done by:

a. Carry out health promotion to the wider community, especially those who are at risk of contracting bird flu such as poultry farmers.

b. Carry out biosecurity, which is an effort to avoid contact between animals and microorganisms, in this case, avian influenza viruses, such as by disinfection and sterilization of livestock equipment that aims to kill microorganisms on livestock equipment so that they do not infect animals.

c. Carry out vaccinations against farm animals to increase their immunity. Vaccination is done by using an inactive HPAI (H5H2) and recombinant vaccine for chickenpox or fowlpox by inserting the H5 avian influenza virus gene into the smallpox virus.

d. Keep poultry livestock pens from living quarters.

e. Use personal protective equipment such as masks, hats, long sleeves, long pants, and boots when entering the farm area.

f. Cook cooked meat before consumption. It aims to kill the virus contained in chicken meat because the results of the study of the bird flu virus died at 60°C heating for 30 minutes.

g. Conducting the mass destruction of animals on farms thatare positively found in the bird flu virus in livestock in large numbers.

h. Do quarantine people who are suspected or positive for bird flu.

i. Conduct surveillance and monitoring that aims to collect reports on morbidity and mortality, field investigation reports, isolation and identification of infectious agents by the laboratory, the effectiveness of vaccination in the population, and other data that is used for epidemiological studies.

C. Secondary Prevention

Secondary prevention is prevention carried out to prevent the onset of disease with early detection and appropriate treatment. By making early detection, disease control can be given early to prevent complications, hinder its journey, and limit the inability that can occur.[11]

This prevention done in the presymptomatic phase and clinical phase. Avian influenza secondary prevention is carried out by screening which is an attempt to actively find the disease in people who have not shown clinical symptoms. Screening for bird flu is done at the airport by installing a body heat detector so people suspected of contracting bird flu can be treated immediately and quarantined so that it is not transmitted to others.[11]

C. Tertiary Prevention

Tertiary prevention is any attempt made to limit capacity. In bird flu, tertiary prevention efforts that can be done is by conducting intensive treatment and rehabilitation.[11]

Until now, antiviral therapy is as early as possible a form of tertiary prevention.[52] There are 4 types of antiviral drugs for the treatment and prevention of H5N1, including amantadine, rimantadine, zanamivir, and oseltamivir (Tamiflu).[53]

Among the 4 types of antiviral drugs, oseltamivir treatment is one of the most reliable therapies.[54]

Oseltamivir is known to shorten the illness and reduce the length of treatment if given within the first 48 hours after onset.[55]

D. Quaternary Prevention

According to Brodersen (2014), quaternary prevention is an action taken to protect individuals or patients who have been infected from medical interventions so that an illness does not recur. Quaternary prevention in bird flu is in the form of keeping poultry cages away from homes. Hold poultry in a cage so as not to catch the disease from other birds, and wear a mask and goggles when in chicken or poultry farms.[2]

GLOBAL PANDEMIC ZOONOSIS FLU

Several zoonotic flu diseases have plagued up to become a global pandemic, namely the H5N1 disease that had the plague in 1997, SARS in 2003, H1N1 in 2009, MERS in 2012, and which is currently being endemic, namely COVID-19 in 2020. The five diseases of zoonotic flu have many differences from one another.

1. Clinical Symptoms

Clinical symptoms in someone suffering from H5N1 disease, (100%) had a high fever >38°C, (86.49%) had a cough, (81.08%) experienced shortness of breath, and (62.16%) experienced malaise.[22,23]

Clinical symptoms in someone suffering from COVID-19 disease, (87.9%) having a high fever >38°C, (67.7%) having a cough and (38.1%) experiencing malaise.[24]

Clinical symptoms in someone suffering from SARS, (100%) have a high fever >38°C, (75%) have a cough, (45%) experience pain in the chest/muscles/joints, and (45%) experience malaise.[25, 26]

Clinical symptoms in someone suffering from MERS disease, (89%) have a high fever >38°C, (89%) have a cough, (56%) have shortness of breath, and (87%) have chills. [27, 28, 29, 30, 31]

Clinical symptoms in someone suffering from H1N1 disease, (93%) had a high fever >38°C, (83%) had a cough, (54%) experienced shortness of breath, and (68.42%) had a runny nose/nasal congestion.[32, 33]

2. Agent Of Diseases

H5N1

The virus that causes bird flu is classified as family orthomyxoviridae. Viruses consist of 3 different antigenic types, namely A, B, and C. Influenza A viruses can be found in poultry, humans, pigs, horses, and sometimes other mammals, such as mink, seals, and whales.[6]

COVID-19

The virus that causes COVID-19 is SARS CoV 2 (Severe Acute Respiratory Syndrome Coronavirus 2). Coronavirus classification is an RNA virus that belongs to the family Coronaviridae, suborder Cornidovirineae, which belongs to the Order of Nidovirales and Riboviria. It is one of 39 species in 27 subgenera, and 5 genera.[34]

SARS

The virus causes SARS is SARS-CoV which is one of 36 coronaviruses in the Coronaviridae family in the order of Nidovirales. Coronaviridae members are known to cause respiratory or intestinal infections in humans and animals. Although there is a clear degree of phylogenetic divergence from other known coronaviruses, SARS-CoV is considered a coronavirus 2b group.[35]

MERS

The virus Mers cause is Mers CoV which is classified in the genus coronavirus in order of Nidovirales. There are 3 main groups of coronaviruses: alpha (α), beta (β), and gamma (γ). The coronavirus causes Middle Eastern Respiratory Syndrome (MERS-CoV) is a beta coronavirus.[36]

H1N1

The virus that causes H1N1 is influenza virus type A. This virus comes from the family Orthomyxoviridae, based on surface hemagglutinin (H) and neuraminidase antigen (N). Type A influenza virus antigens can undergo two types of changes or mutations, namely: antigenic drift if the mutation occurs slowly and antigenic drift that occurs suddenly.[37]

3. Pathogenesis

Influenza A / H5N1 virus is very virulent and contagious. Initially, transmission only occurred between wild birds and spread among livestock poultry through equipment, transport equipment, food, pens, and clothing. After an outbreak of avian influenza infection in poultry, this virus can spread from birds to humans. This influenza A virus can cause a pandemic because it is easily mutated, either in the form of antigenic drift or antigenic shift to form new variants that are more pathogenic.[9]

For infections produced by H1N1 occur in the upper or main airways of the body. During the 2009 pandemic, evaluation of tissue samples from fatal cases showed the H1N1 virus infects

cells in the lungs. The study also shows that early evidence of bacterial pneumonia contributes to deaths related to H1N1. Pathologists determine microscopic examination of tissue can be used to identify bacterial co-infection after death.[38]

In 2012, a new type of Coronavirus was discovered in the Middle East under the name MERS-CoV. Although MERS and SARS clinically have the same thing. However, the difference between the two is very clear. MERS with the genus Betacoronavirus, with the subfamily Coronavirinae, the Coronaviridae family, and the sequence Nidovirales. MERS tends to be less infectious than SARS. MERS is thought not to spread easily from human to human but has a high mortality rate of around 40%.[39]

In the SARS-CoV study, the S protein binds to the receptor in the Host cell, the enzyme ACE-2 (angiotensin-converting enzyme 2). ACE-2 can be found on the oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, large intestine, skin, thymus, bone marrow, spleen, liver, kidney, brain, pulmonary alveolar epithelial cells, small intestine enterocyte cells, arterial endothelial cells, veins, and smooth muscle cells. After successfully entering the next is the translation of gene replication of the viral RNA genome. Furthermore, replication and transcription where the RNA virus synthesis through translation and assembly of the virus replication complex. The next step is the assembly and release of virus.[40]

After transmission, the virus enters into the upper respiratory tract and then replicates in the upper respiratory tract epithelial cells. Then spread throughout the entire breath. In acute infections, the virus decays from the airways and can continue to decay for some time in the gastrointestinal cells after healing. The incubation period for the virus to appear around 3-7 days.[41]

This new type of Coronavirus can transmit from bats to humans which cannot yet be identified. New Coronaviruses produce a variety of new antigens and the population does not have immunity to virus mutant strains that can cause pneumonia. In this case, "super-spreader" cases are found where the virus mutates or adapts in the human body so that it has a very strong and very infectious transmission power.[41]

In SARS-CoV-2 it was found that the target cell was likely to be in the lower airway using ACE-2 as the same receptor as SARS-CoV. Sequences of RBD (Receptor Binding Domain) include RBM (Receptor Binding Motif) on SARS-CoV 2 in direct contact with the ACE2 enzyme. The

residual results in SARS-CoV2 RBM (Gln493) interact with ACE2 in humans, consistent with the capacity of SARS-CoV2 for human cell infection.[42]

4. Distribution Of Person, Place and Time (Shown in Table.3)

5. Chain Of Infection

COVID-19

The Chain transmission of COVID-19 (shown in **Fig. 3**) consists of an Exit Portal of this disease that is through the respiratory system/airway, such as coughing or sneezing and is therefore at risk of having the mucosa (mouth and nose) or conjunctiva (eye) exposed to potentially infective respiratory droplets. From the results of phylogenetic analysis, the reservoir of this disease is thought to be a bat. The COVID-19 transmitted through droplets and close contact with people infected with the disease is not believed but can considered if certain aerosol-producing procedures are carried out at a health facility. The transmission of this virus in the scope of households, from human to human, the statement was strengthened by data from the Guangdong province of China which found as much (78% -85%) COVID-19 occurred in families. This virus entry portal through the respiratory / airway system.[43, 44, 45]

H1N1

The H1N1 chain of transmission through the Portal Exit of this disease has flu-like symptoms in general that come out of the body through the mouth and nose (shown in **Fig. 4**). Coughing and sneezing become a means of transmission of this disease because the resulting droplet contains the virus. The reservoir of H1N1 or swine flu is swine. In transmission mode, this virus is transmitted indirectly through air or airborne. Portal Entry of this virus that is the entry of the virus into the body through every hole in the body can directly provide access into cells through the eyes, mouth, and nose.[46]

MERS

MERS Transmission Chains from the Exit Portal through the respiratory system or airway. Reservoirs in this disease are bats and camels. The transmission mode in this disease virus spreads from the respiratory secretions of an infected person, through the sufferer's cough. This virus can also spread from sick people to other people through close contact such as when treating people infected with the virus, it is very easy for transmission to occur in places such as health facilities. Portal Entry of this disease also through the respiratory system or airway that shown in **Fig. 5**.[47]

SARS

SARS transmission chain (shown in **Fig. 6**) from the Exit Portal Through the respiratory system or airway. Reservoirs in this disease are bats and mongoose. The transmission mode of this deadly virus is thought to be mediated mainly through droplets containing the virus. And also the transmission of this virus through aerosols or small particles and feces and directly or indirectly the virus will enter if there is direct or indirect contact with others, the virus will enter the lungs (as its main pathological target). The portal entry of this virus through the respiratory system or airway.[48, 49]

H5N1

The H5N1 transmission chain starts from the Exit Portal where the virus is released by the host through nasal fluid or feces. Reservoirs in H5N1 are birds and other birds. Mode of transmission in this disease virus through inhalation and direct contact. Most cases of this virus infection in humans are caused by the transmission of the virus from poultry to humans. Apart from direct contact with infected birds, feeding animals such as cats, tigers, and other animals with infected birds, it is proven that these animals can experience lung disorders in the form of pneumonia, severe diffuse alveolar damage, and even death. Transmission of this virus can also occur in children when swimming in contaminated water and if swallowing food or drinks contaminated with avian influenza virus. Exit portal of this virus through the respiratory tract, digestive tract, and conjunctiva that shown in **Fig. 7**.[50, 51]

4. CONCLUTION

H5N1 is a disease caused by influenza A virus that can found in poultry, humans, pigs, horses, and sometimes other mammals, such as mink, seals, and whales. H5N1 became a global pandemic in 1997. 5 zoonotic flu diseases have become a global pandemic namely H5N1, SARS, H1N1, MERS, and COVID-19. The five diseases have differences ranging from disease agents, clinical symptoms, pathogenesis, distribution of people at the time, and the chain of transmission.

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Clinical Symptoms	H5N1	COVID-19	SARS	MERS	H1N1

Fever	**100%**	**87,9%**	**100%**	**89%**	**93%**
Cough	**86,49%**	**67,7%**	**75%**	**89%**	**83%**
Chest Pain / Muscle Pain / Joint Pain	**5,41%**	**14,8%**	**45%**	**44%**	**36%**
Diarrhea	**16,22%**	**3,7%**	**25%**	**26%**	**24%**
Shortness of Breath	**81,08%**	**18,6%**	**40%**	**56%**	**54%**
Malaise	**62,16%**	**38,1%**	**45%**	**33%**	**40%**
Headaches	**21,62%**	**13,6%**	**20%**	**11%**	**31%**
Siver	**1,8%**	**11,4%**	**15%**	**87%**	**37%**
Nausea / Vomiting	**37,84%**	**5%**	**35%**	**21%**	**29%**
Colds / Nasal Congestion	**37,84%**	**4,8%**	**15%**	**13%**	**68,42 %**

Table 2. Differences in Agent of Global Pandemic Zoonosis Flu

Agent	H5N1	COVID-19	SARS	MERS	H1N1
	Influenza A Virus	SARS CoV-2	SARS-CoV	MERS-CoV	Influenza type A Virus

Table 3. Differences in Distribution Person, Place and Time of Global Pandemic Zoonosis Flu

Variabel	H5N1	COVID-19	H1N1	MERS	SARS
Person					
Age	<40 years old and <20 years old.	51 years old.	5-45 years old.	49,5 years old dan elderly >60 years old.	Adult : >65 years old. Young : 35-64 years old.
Sex	Male and Female.	Male.	Pregnant Woman.	Male.	Female.

Job/ Health Worker	Breeders.	Laborers, farmers and health workers	Breeders	Traders of animal and fish.	Travelers and health workers.
Immunity	Low immunity and Co-morbid.	Low immunity and Co-morbid.	Low immunity and Co-morbid.	Low immunity.	Low immunity.
Place					
First Detected	Hong Kong.	Wuhan, Hubei Proince of China.	The United State Of Amerika.	Saudi Arabia (Jeddah).	Guangdong, China.
Time					
Pandemic Year	1997.	2020.	2009.	2012.	2003.