http://ejournal.seaninstitute.or.id/index.php/healt
Jurnal eduhealth, Volume 13, No 02, 2022
E-ISSN., P-ISSN. 2087-3271

Analysis of the Effectiveness of Avian Influenza Treatment in Humans: Literature Review

Rika Valensia[1], Indah Laily Hilmi[2], Salman[3]
[1,2,3] Universitas Singaperbangsa Karawang, Karawang, Indonesia

ARTICLE INFO

Keywords:
Avian Influenza, effectivity, oseltamivir.

ABSTRACT

Avian influenza is an influenza disease that is transmitted from birds, can transmit to humans and then can also be transmitted between humans, so that it can cause epidemics. Avian influenza is caused by a myxovirus virus that belongs to the *Orthomyxoviridae* family. This disease can be treated with antivirals and various other complementary drugs. These variations were then compared with a systematic literature review method to see which treatment had the best effect on treating avian influenza. The sample used in the research was taken from the population or individuals (case study). Results: most patients were treated with oseltamivir, some were given other antivirals and other additional treatments. Conclusion: treatment using the antiviral oseltamivir given ≤ 2 days after the onset of symptoms showed better treatment effectiveness than using other antivirals and corticosteroids.

Email :
rikavalensia@gmail.com
indah.laily@fkes.unsika.ac.id
salman.kes@fikes.unsika.ac.id

1. INTRODUCTION

Myxovirus virus is a virus that causes influenza disease. Influenza is a disease that is easily transmitted. The symptoms of influenza experienced by patients vary greatly depending on the immune system or body resistance of each individual, including fever, cold cough, sneezing, watery eyes, soreness and muscles. The disease can be transmitted through sneezing, coughing, and others. Influenza has three types, namely type A which is epidemic which can cause a spread event or become an outbreak in an area, type B with a milder disease than A but sometimes it can cause epidemics, and type C which is uncertain can cause influenza in humans [1]. Type A influenza should be watched out for because it is the only type of Influenza that can become a pandemic so that it affects world health. Type A influenza is further divided into subtypes based on differences in the combination of hemagglutinin (HA) and neuraminidase (NA) glycoproteins present on the surface of the virus. The HA subtype works to regulate the ability of viruses to enter cells and then reproduce themselves. What is included in the influenza virus type A infection is avian influenza virus infection or Avian Influenza Virus (AIV) which originates from poultry then mutates and can be transmitted from person to person [2].

So far there have been 18 HA (H1-H18) and 11 NA (N1-N9) subtypes. Birds are growing strains of influenza A virus that can further infect all other animals and humans. H5N1 avian influenza virus is a virus that can be transmitted directly from birds to humans, the H9N2 virus strain in humans causes relatively mild symptoms and can attack pigs as an intermediary for poultry-to-human transmission, the H7N9 strain first appeared in China in 2013 which caused human-to-human infection with wide transmission, a higher mortality rate and more severe than other H7 viruses [3]. The total number of cases that occurred on May 31, 2013 in China was 132 people infected with this virus and 39 people experienced fatal cases because of it [4]. From January 2003-February 2022, globally the A5N1 avian influenza virus was reported to have infected 863 humans from 18 countries with 455 of them fatally occurring (CFR 53%). The H5 and H7 avian influenza virus subtypes have the potential to change from initially low-pathogenic to highly pathogenic, this is because some gene segments of these subtypes are easily exchanged to produce new viruses or mutations into dangerous and very deadly versions [2], [3]. In the H5N6 strain, from 2014-2022, there have been 66 reported cases of infection with this type of

virus with 29 deaths occurring. There was only one case of human infection of the H7N4 strain virus reported in 2018. Globally, in the H7N9 strain reported from 2013-2022 there were 1568 infected humans including 616 fatal cases (CFR 39%). Of the 1568 people infected, 33 of them reported a hemagglutinin gene mutation that showed the pathogenicity of poultry turned high. H9N2 subtype infection reported from December 2015-February 2022 there were 21 infected people with 2 people dying (accompanied by underlying conditions) [5]. Highly pathogenic avian influenza viruses (HPAIV) can cause cytokine storms and multiorgan failure. HPAIV can elicit systemic inflammatory response syndrome in infections and eventually lead to death from multiorgan failure. The highest viral load is found in the lungs and epithelium of the alveolus. In the lungs, a strong infiltration of macrophages derived from the blood of infected patients with a high amount of cytokines in the blood [6]. Diagnosis of avian influenza laboratory examination in patients can use the real-time Reverse Transverse Polymerase Chain Reaction (RT-PCR) method according to WHO recommendations or use a biosensor method that can detect influenza A virus within 10 minutes after the sample is inoculated [7]. Avian influenza treatment can use antiviral drugs such as oseltamivir and symptomatic drugs to treat the symptoms experienced, including dehumidifiers, antibiotics, and others [8].

Based on this exposure, the writing of this review article is intended to see that the use of drugs in avian influenza patients has been appropriate and correctly effective in overcoming avian influenza disease in several populations and individuals in humans.

2. METHOD

The method employed in this review literature is systematic literature review that identifies, evaluates, and interprets all available research that is relevant to a particular research question, topic area, or phenomenon of interest. Literature studies are taken from various articles or journals with a span of the last 10 years regarding theories that are relevant to the content of the topic of discussion, namely the treatment of avian influenza. The literature was taken by conducting an internet search from Google Scholar, PubMed, and Science Direct using the keywords " avian influenza " "treatment for avian influenza" and "antiviral for avian influenza". Inclusion criteria are of all sexes (male and female) with any condition (pregnant or with comorbidities), without a specific age range, are experiencing or have had avian influenza. The review studied was the drugs given and their effects on patient recovery were then compared between one literature and another. The exclusion criterion is avian influenza in animals. From the search, 6 literature was obtained that discussed cases of avian influenza that occurred in populations or individuals. The authors seek to compare the effectiveness of the use of drugs in patients infected with the avian influenza virus with different strains so that conclusions can be drawn on treatments that have better effectiveness.

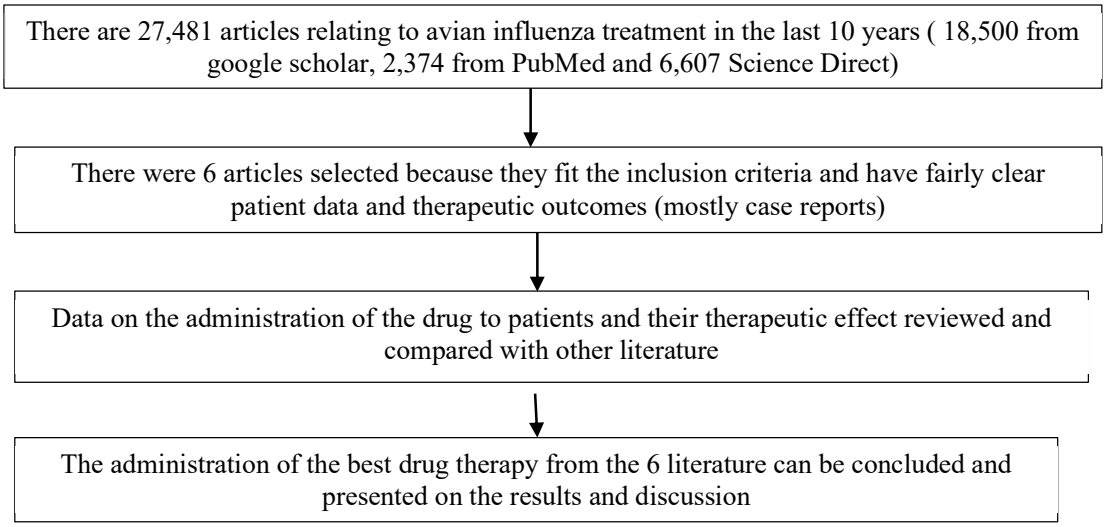

Figure 1. Methodology

3. RESULTS AND DISCUSSION

Flu viruses belong to the family Orthomyxoviridae and contain thousands of different antigenic subtypes. The virus is highly pathogenic, first isolated from domestic geese in China in 1996, subsequently following other cases in domestic birds, wild birds and humans in more than 60 countries. The virus can be spread from poultry to humans but not vice versa [9]. This virus is not only detected in poultry farms but also in traditional markets that sell poultry and poultry products. In a study conducted by Hewajuli, et al (2017) avian influenza viruses can be transmitted through feces, cloaca and trachea in poultry. The release of the virus through poultry feces occurs over a longer period of time than through the cloaca and trachea, which is 28 days, where the longer the excretion period, the greater the spread of the virus. Most avian influenza positive samples come from cloacal swabs from birds that do not show clinical symptoms of illness, whereas through fecal excretion it is likely to contaminate and persist in the environment in large numbers at certain times and conditions. Research shows that avian influenza viruses can be damaged after exposure to ultraviolet light radiation. Virus sampling in dry and rainy season areas shows that the rainy season has the potential to spread the virus more through rainwater holes infected with poultry feces and this virus can last longer because during the rainy season exposure to ultraviolet rays is less, feces remain fresh and moist for 14 days [10].

Treatment avian influenza usually uses antivirals because the disease is caused by a virus. However, some hospitals provide different antivirals or medications with different patient conditions. The following are the results of a literature study of the use of the drug for avian influenza positive patients in several hospitals and its effectiveness:

Table 1. The Effectiveness of Avian Influenza Drugs Against Populations and Individuals in Humans

No	Reference	Research Samples	Result
1	(Chan et al, 2012) [11]	407 male patients aged 0-14 years were confirmed to be infected with H5N1 from laboratory results. The study was conducted by looking at the differences in pharmacological therapy obtained and the time of administration in patients.	Children aged 0-5 years have a lower mortality rate than the elderly. Oseltamivir given 2 days after the onset of symptoms showed a greater survival impact than patients who received 3-5 days later and patients who were not given oseltamivir. Additional treatment with antibiotics showed no effect nor the use of corticosteroids may increase CFR values.
2	(Qi et al, 2014)[12]	Women aged 25 years, 17 weeks gestational age show symptoms of infection with avian influenza virus A (H7N9). Given mechanical ventilation, oseltamivir drugs (150 mg/day for a week), gamma-globulins, antifibrotic therapy (glutathione), and nutritional support.	X-rays showed extensive infiltrates in both lungs, the condition stabilized and improved gradually. The patient is then discharged in good health without fetal abnormalities. Patients after recovering experience the same viral infection again, research suggests that pregnancy may be a high risk factor for being infected with the H7N9 virus.
3	(Tang et al, 2015)[13]	A 61-year-old woman was diagnosed with severe pneumonia caused by the A7N9 avian influenza virus. Intravenous treatment of peravimir, imipenem/cilastin, teicoplanin and caspofungin is given. The patient	The patient's clinical symptoms improve gradually, oxygenation and chest x-rays are significantly improved. Day 13 of VV-ECMO therapy was stopped, but CVVH therapy continued because kidney function had not recovered.

		experienced acute renal failure so he was given continuous veno-venous hemo (CVVH) filtration. Patients are also given breathing assistance using venovenous (VV) extracorporeal membrane oxygenation (ECMO). The patient is not given glucocorticoids.	
4	(Cao et al, 2016) [14]	Teenager and adult patients aged >14 years with influenza A virus infection (H7N9). There were 288 hospitalized patients with viral pneumonia H7N9 was registered in the study for analysis.	The use of corticosteroids in H7N9 virus pneumonia at high doses may increase patient mortality, whereas at low doses it should be further explored using larger databases or RCTs.
5	(Ma et al, 2018) [15]	- 25 patients aged >18 years (have been discharged from the ICU), observed blood samples at 100, 200, and 300 days after the onset of symptoms. All patients received oseltamivir and 21 received glucocorticoids for treatment. - 10 control subjects of people living in the area, not detected H7N9 virus, not close to live birds for the previous 12 months, and had no disease or condition that could reduce their immune response.	- Survivors have antibody titers equal to or greater than the seroprotection threshold (≥1:40 for HI, NI, and MN) or a minimum detection limit (1:400 for IgG and 1:50 for IgA) at each point in time. - Respondents' antibody responses varied widely and some had weak antibody responses or rapidly reduced antibody titers that went undetected 1 year after infection despite severe infection.
6	(Le et al, 2019)[16]	The patient is 26 years old, working as a farmer, 36 weeks gestational age with symptoms of fever and cough. Patients are initially treated with antibiotics and antipyretics. The patient tested positive for avian influenza virus A (H5N1) after RT-PCR examination. After birth, the patient's baby is also examined whether it is exposed to infections such as baby's mom or not.	New patients are given oseltamivir 5 days after symptoms appear, in contrast to WHO guidelines which recommend that patients with suspected influenza should receive oseltamivir as early as possible to reduce mortality, antivirals can be viral protection (H5N1) when administered 48 hours after symptoms develop. The patient dies 6 days after symptoms develop. Meanwhile, in the baby, the throat swab results showed negative influenza viruses A(H5), A(H3), B, and A(H1) pdm09.

Based on table 1, it is known that most of the antivirals used for the treatment of avian influenza infections are oseltamivir. Patients who received oseltamivir faster showed better treatment effectiveness, as can be seen in the study conducted by Chan, et al (2014) where patients who received oseltamivir within 2 days showed better survival than those who received it on day 3 to 5. In a study conducted by Le, et al (2018) also showed that the delay in administering oseltamivir in pregnant patients positive for avian influenza had an impact on death [11], [16]. This is in accordance with the Avian Influenza Guidelines where antivirals such as oseltamivir in the treatment of avian influenza

should be given immediately because of its effectiveness 48 hours after the onset of symptoms. Oseltamivir is given to people who come into contact with suspected patients such as, health workers and laboratory personnel who do not use PPE in handling samples containing avian influenza virus [8]. The study also showed that treatment using oseltamivir is better than using other antibiotics. Amantadine (Symmetrel) and rimantadin (Flumadine) are the first generation of antiviral drugs that initiated influenza treatment as prevention and management. However, both drugs are no longer effectively used for influenza treatment due to the large number of resistant cases so for now oseltamivir is used which is a second generation drug and is the only treatment for influenza. Oseltamivir is an influenza first-line antiviral drug by inhibiting neuraminidase (NA) found on the surface of influenza viruses [17]. From the table data, it is also stated that corticosteroids or glucocorticoids are used to treat the symptoms caused by influenza. Corticosteroids or glucocorticoids are the most effective anti-inflammatory drugs and are the most widely used as adjuvant therapies [18]. Treatment with corticosteroids shows no better than a single therapy of oseltamivir. Corticosteroids can increase CFR values and trigger patient mortality so it is necessary to consider their use for avian influenza patients [11], [14]. According to Ma's research, et al (2018) the antibody responses of patients who have recovered are very diverse, even some are not detected even though the influenza experienced is severe. This allows the patient to catch the flu again [15]. As in the study of Qi, et al (2014) that patients get the same virus again after being declared cured. Pregnant patients are also at high risk of contracting it so pregnant women are prioritized to undergo vaccines as a preventive measure. Although the baby in the womb is not infected from the mother who has tested positive for avian influenza, it is necessary to conduct further analysis on the matter [12]. Vaccines are an effective strategy to prevent the occurrence of avian influenza pandemics and prevent the mixing of the genetic material of influenza A viruses with seasonal influenza viruses, it is necessary to provide prepandemic vaccines and pandemic vaccines [8].

4. CONCLUSION

Based on the results of literature study data on the effectiveness of avian influenza treatment in humans with different circumstances and therapeutic administration, it can be concluded that the best therapy can use oseltamivir antivirals that are consumed as soon as possible, namely a maximum of 2 hours after the initial symptoms of avian influenza appear. It is appropriate based on the guidelines that oseltamivir is used as the first line of treatment of avian influenza. The administration of corticosteroids as an adjunct therapy needs further consideration because it can increase CFR values and patient mortality. Patients with pregnant conditions are more at risk of being infected with the avian influenza virus, but not necessarily the fetus or baby conceived will contract the virus from the mother. Avian influenza is an infectious disease that can cause epidemics so it needs proper prevention and treatment to reduce the incidence of infection and resistance to antivirals.

REFERENCES

[1] A. Nashrullah and M. Kharis, "Pemodelan Sirs Untuk Penyakit Influenza Dengan Vaksinasi Pada Populasi Manusia Tak Konstan," *UNNES Journal of Mathematics*, vol. 2, no. 1, pp. 46–54, 2013, doi: https://doi.org/10.15294/ujm.v2i1.1711.

[2] K. Chávez Ramos *et al.*, "Rapid, Sensitive, and Selective Detection of H5 Hemagglutinin from Avian Influenza Virus Using an Immunowall Device," *ACS Omega*, vol. 4, no. 15, pp. 16683–16688, Oct. 2019, doi: 10.1021/acsomega.9b02788.

[3] B. Taye *et al.*, "A System Based-Approach to Examine Host Response during Infection with Influenza A Virus Subtype H7N9 in Human and Avian Cells," *Cells*, vol. 9, no. 2, Feb. 2020, doi: 10.3390/cells9020448.

[4] J. Zhou *et al.*, "Biological features of novel avian influenza A (H7N9) virus," *Nature*, vol. 499, no. 7459, pp. 500–503, 2013, doi: 10.1038/nature12379.

[5] World Health Organization [WHO], "Avian Influenza Weekly Update Number 830 Human infection with avian influenza A(H5) viruses Human infection with avian influenza A(H5N1)

virus," Feb. 2022. [Online]. Available: https://www.who.int/teams/global-influenza-programme/avian-influenza/monthly-risk-assessment-

[6] J. Friesenhagen *et al.*, "Highly pathogenic influenza viruses inhibit inflammatory response in monocytes via activation of rar-related orphan receptor RORα," *J Innate Immun*, vol. 5, no. 5, pp. 505–518, Jul. 2013, doi: 10.1159/000346706.

[7] J. Lin *et al.*, "An impedance immunosensor based on low-cost microelectrodes and specific monoclonal antibodies for rapid detection of avian influenza virus H5N1 in chicken swabs," *Biosens Bioelectron*, vol. 67, pp. 546–552, May 2015, doi: 10.1016/j.bios.2014.09.037.

[8] Kementerian Kesehatan Republik Indonesia, *Pedoman Penanggulangan Flu Burung*. Jakarta: Kemenkes RI, 2017. [Online]. Available: https://www.researchgate.net/publication/327414412

[9] S. K. Jha, R. Thapa, P. K. Gupta, D. Neupane, S. Shrestha, and A. Gupta, "Knowledge, attitude and practice related to Avian influenza among poultry workers of Kathmandu, Nepal," *Int J Community Med Public Health*, vol. 9, no. 1, p. 76, Dec. 2021, doi: 10.18203/2394-6040.ijcmph20214984.

[10] D. A. Hewajuli, N. L. P. I. Dharmayanti, and I. W. T. Wibawan, "Deteksi, Isolasi, dan Identifikasi Avian influenza Subtipe H5N1 pada Unggas di Pulau Jawa, Indonesia Tahun 2016," *Jurnal Veteriner*, vol. 18, no. 4, pp. 496–509, Feb. 2018, doi: 10.19087/jveteriner.2017.18.4.496.

[11] P. K. S. Chan *et al.*, "Determinants of antiviral effectiveness in influenza virus a subtype H5N1," *Journal of Infectious Diseases*, vol. 206, no. 9, pp. 1359–1366, Nov. 2012, doi: 10.1093/infdis/jis509.

[12] X. Qi *et al.*, "Avian Influenza A(H7N9) Virus Infection in Pregnant Woman, China, 2013," *Emerg Infect Dis*, vol. 20, no. 2, Feb. 2014, doi: 10.3201/eid2002.131109.

[13] X. Tang *et al.*, "ARDS associated with pneumonia caused by avian influenza A H7N9 virus treated with extracorporeal membrane oxygenation," *Clinical Respiratory Journal*, vol. 9, no. 3, pp. 380–384, Jul. 2015, doi: 10.1111/crj.12140.

[14] B. Cao *et al.*, "Adjuvant corticosteroid treatment in adults with influenza a (H7N9) viral pneumonia," *Crit Care Med*, vol. 44, no. 6, pp. e318–e328, Jun. 2016, doi: 10.1097/CCM.0000000000001616.

[15] M. J. Ma *et al.*, "Influenza A(H7N9) virus antibody responses in survivors 1 year after infection, China, 2017," *Emerg Infect Dis*, vol. 24, no. 4, pp. 663–672, Apr. 2018, doi: 10.3201/eid2404.171995.

[16] T. van Le *et al.*, "Fatal avian influenza A(H5N1) infection in a 36-week pregnant woman survived by her newborn in Sóc Trăng Province, Vietnam, 2012," *Influenza Other Respir Viruses*, vol. 13, no. 3, pp. 292–297, May 2019, doi: 10.1111/irv.12614.

[17] V. Setiawaty, H. Apsari Pawestri, and Ketut Susilarini, "Deteksi Resistensi Oseltamivir Influenza A (H1N1pdm09) dari Pasien Infeksi Saluran Pernafasan Akut Berat di Indonesia tahun 2014," *Jurnal Kefarmasian Indonesia*, vol. 6, no. 1, pp. 16–22, 2016.

[18] M. A. Darmadi and G. Singh, "Efektivitas Kortikosteroid Sebagai Terapi Adjuvan Pada Pneumonia Komunitas Berat: Laporan Kasus Berbasis Bukti," 2017.