Avian Influenza Virus Endemicity During the Covid-19 Pandemic in Indonesia

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Abstract. The covid-19 pandemic that occurred in the beginning of 2020 has affected all sectors, particularly in health and economic sectors. The Avian Influenza Virus (AIV), a zoonotic virus that have been reported endemic in Indonesia since 2003, might be affected by this condition. There is very limited information related AIV distribution and circulation due to covid-19 pandemic in Indonesia. This study aims to investigate the endemicity of the AIVs in Indonesia by conducting surveillance in several districts/cities in Central Java, West Java, Yogyakarta, and East Java Provinces during 2021. The samples were tested using the RT-PCR method and then DNA sequencing was carried out at Hemagglutinin and Matrix genes. The results of this study were obtained from 597 pool and individual samples from cloacal swabs, tracheal swabs, organs, and environmental swabs of poultry obtained from live poultry markets and poultry farms. The result revealed that 105 samples were tested positive for Influenza A (Matrix). Furthermore, AIV subtype-specific reverse transcription polymerase chain reaction (RT-PCR) from 105 samples tested positive for Influenza A showed that 4 samples tested positive for subtype H5 (3.8%), 4 samples tested positive for subtype H9 (3.8%), 8 samples tested positive for subtype H3 (7.6%), and no samples was found positive for subtype H10. The results showed that the AIV subtype H5N1 still circulating in Indonesia, interestingly the H3 subtype was found to be the predominant virus in this study. Influenza virus subtype H3 has a very diverse host range from birds to various mammalian species including pigs, horses, and dogs, and causes sporadic outbreaks in marine mammals. After the emergence of the A/Hong Kong/1968 (H3N2) pandemic virus, it became endemic and caused annual seasonal epidemics in humans. In China, Influenza virus subtype H3 has had a lineage in domestic poultry and has several subtypes that are H3N2, H3N3, H3N6, and H3N8, which have been isolated from domestic poultry globally. The infection of Influenza virus H3 Subtype can cause mild to severe disease. Experimental studies have also shown that the H3N8 subtype virus originating from poultry can replicate in the respiratory tract of mice, indicating that H3 isolates pose a threat of zoonotic infection. Therefore, the monitoring of H3 subtype AIVs and other AIVs subtype raised great concerns related to the potential threat to animal and human health and poses a potential risk to public health.

Keywords: avian influenza virus · reassortment · zoonoses

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1 Introduction

Avian Influenza Virus (AIV) is a type A influenza virus from the Orthomyxoviridae family. The AIV genome is a negative-sense single-stranded RNA with 8 segments encoding 10 proteins including Polymerase Acid (PA), Polymerase Base (PB1 and PB2), Nucleoprotein (NP), Hemagglutinin (HA), Neuraminidase (NA), Matrix (M1 and M2) and Non-Structural (NS1 and NS2). Influenza A virus subtypes can be categorized based on the HA and NA genes [1]. Meanwhile, based on its pathogenicity in causing disease and death in chickens and its molecular characteristics, AIV can be divided into low pathogenicity avian influenza (LPAI) and highly pathogenic avian influenza (HPAI) [2, 3]. H5N1 influenza virus is classified as a zoonotic virus that can have serious impacts on animal and human health, and can cause severe symptoms and high mortality with a case fatality rate of 84% (There were 168 deaths in 200 confirmed cases) [4]. The current epidemic of H5N1 highly pathogenic avian Influenza in Southeast Asia raises serious concerns that genetic reassortment will result in the next Influenza pandemic [5].

Since pandemic the coronavirus disease 2019 (covid-19) has been occurring in the world including in Indonesia caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [6]. As of June 4, 2022, confirmed cases of covid-19 in Indonesia reached 6,046,467 cases with a death rate of 156,240 (2.6%). The covid-19 pandemic has caused significant loss in various sectors, especially in the livestock sector. The covid-19 pandemic potentially affects poultry consumption, as well as the poultry farming economy and the circulation/endemicity of other viruses circulating in the field.

The ongoing covid-19 pandemic may have an impact on research activities and sample surveillance in the field.. As a result, information regarding the circulation and evolution of AIV in the field is very limited. Some recent reports showed that the new reassortant virus such as AIV H9N2 which experienced reassortant with the PB2 gene of the H5N1 virus was found in Indonesia since 2018 [7–9] and previously some H5N1 mutation and reassortant have detected in some areas in Indonesia [10–13]. Both mutation and reassortment give rise to genetic diversity which may have an impact on the alteration various aspects of virus biology, such as pathogenicity, infectivity, transmissibility and/or antigenicity [14]. The mutation virus, including reassortant virus, decreased the effectiveness of the vaccine. The proper vaccine is expected to reduce clinical symptoms, economic losses and virus shedding due to AI infection. The decrease in virus shedding will reduce viral contamination in the environment, thereby reducing the risk of humans contracting the virus. Monitoring the circulation of the avian influenza virus is expected to continue even in the covid-19 pandemic situation. The reassortment of AIV H5N1 with the human H3N2 virus have been reported at the NS gene level [15]. In 2012, H5N1 and LPAI reassortant viruses was reported to cause changes in the pathogenicity of the particular virus. Likewise, in 2018 the H9N2 reassortant virus changed its pathogenicity to be more pathogenic compared to the wildtype H9N2 virus [9]. It seems the evolution of AIV in the future will be dominated by the reassortant AIV. As a result, surveillance is required as a control measure to anticipate changes in the phenotype, particularly in terms of its adaptation to humans and as an early warning system to the next pandemic due to avian influenza variants.

2 Materials and Methods

2.1 Sample Collection

During the covid-19 pandemic, virus circulation was monitored in the field. Samples were collected from traditional markets, live bird markets, and commercial poultry farms in the Java Island. The types of samples taken were serum, cloacal swabs, organs, and the environmental swabs. The sample was taken from the areas of Yogyakarta (Yogyakarta city), West Java (Cianjur Regency), Central Java (Semarang City, Surakarta City and Magelang Regency), and East Java (Lamongan Regency, Surabaya City, Sidoarjo Regency, and Gresik Regency) Province. The purpose of the field activity is to collect swab samples (cloaca/trachea/organs and blood serum) from the market environment or from healthy and sick poultry. Swab samples were placed in transport medium (Dulbecco's modified Eagle's medium; GIBCO, Thermo Fisher Scientific, USA) and portable refrigerator freezer (−20 °C) was used to store samples during the trip to the Indonesian Research Center for Veterinary Science, Bogor, Indonesia. Field samples were then processed in the IRCVS virology laboratory to identify the presence of AI virus using the RT-PCR technique [16–19]). Positive PCR results will be followed by virus isolation in SPF eggs aged 9–11 days. Serum samples will be tested for Hemagglutinin Inhibition (HI).

2.2 Extraction of Viral RNA, RT-PCR

Viral RNA obtained from infected allantoid fluid was extracted using the QIAamp DNA Mini kit (Qiagen, Hilden, Germany) as per the manufacturer's instructions. AIV subtyping was performed on samples that indicated positive for influenza A [17], but negative with the three H5-specific primers designed by Lee et al. [18]; Dharmayanti et al. [19] which were then identified with specific primers H9, H3 and H10. RT-PCR was carried out using a 9800 Fast Thermal Cycler Applied Biosystems machine (Qiagen, Hilden, Germany) with the Superscript III One-Step RT-PCR system by Life Technologies (Waltham, MA, USA), using a 10 μL RNA reaction mixture as a template, 2 μL for each primer, 1 μL Taq Polymerase enzyme, 25 μL PCR Master Mix (2X), and NFW (nuclease-free water) up to 50 μL.. RT-PCR was performed using thermal cycling conditions at an initial denaturing temperature at 42 °C for 45 min; 95 °C for 3 min; denaturation at 95 °C for 30 s; annealing at 50 °C for 40 s; extension at 72 °C for 40 s (35 cycles); and final extension at 72 °C for 10 min. The amplicon was separated with 1.0% agarose gel electrophoresis and visualized with a transilluminator.

2.3 DNA Sequencing

The QIAquick Gel Purification System (Qiagen, Hilden, Germany) was used to purify the specific band. Furthermore, the results of DNA purification were carried out with two-way Direct Sequencing with an ABI PRISM BigDye Terminator Cycle Sequencing Ready Reaction Kit 2.0 (Applied Biosystem, Foster City, CA, USA) using the 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) machine. The sequencing results were verified and edited using BioEdit Version 7.1.3.0. The DNA sequences of the viruses were determined using Basic Local Alignment Search Tool (BLAST) analysis

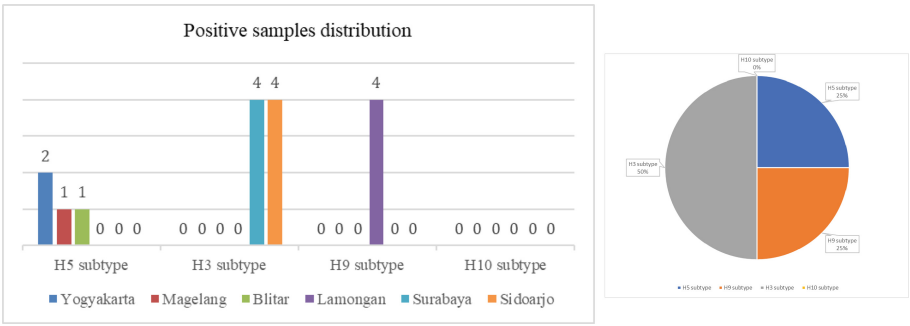

Fig. 1. Distribution of samples that tested positive for subtypes H5, H3, H9 and H10.

(http://www.ncbi.nlm.nih.gov). The phylogenetic tree was generated using the MEGA 5.2. Software package (www.megasoftware.net). Bootstrap analysis with 1000 bootstrap replicates was used to test each phylogenetic analysis. The evolutionary histories of the viruses were concluded using a maximum likelihood calculation based on the Tamura–Nei model.

3 Results

The results of this study obtained from 896 poll samples and individual tracheal swabs, cloacal swabs, organs, of poultry, environmental swabs collected from live poultry markets and poultry farms in Surakarta City, Yogyakarta City, Semarang City, Magelang Regency, Cianjur Regency, Sidoarjo Regency, Gresik Regency, Blitar Regency and Lamongan Regency (Fig. 2). Of the 896 samples obtained, 597 of them were tested for Influenza A (Matrix) with the result that 105 samples were positive for Influenza A.

Subtyping of Avian Influenza H5, H9, H3 and H10 was carried out on 105 samples tested positive for Influenza A with the results 4 positive samples tested positive for AI subtype H5 (3.8%), 4 samples tested positive for AI subtype H9 (3.8%), 8 samples tested positive for AI subtype H3 (7.6%) and no samples were found to be positive for AI subtype H10 (0%) (Fig. 1). Two of the four positive samples of the H5 subtype were found in live poultry markets in Yogyakarta City which one sample collected from Muscovy duck and one another sample collected from duck. Another sample that tested positive for subtype H5 was found in live bird market in Magelang Regency, which was collected from Muscovy ducks while the other sample was obtained from an outbreak case in poultry farm in Blitar Regency.

For all sample tested positive for H9 were obtained from traditional market in Lamongan Regency, three of them were collected from environmental swabs (knives, cutting boards, and napkin/towel) and one sample collected from duck. In this study, Influenza H3 was found to be dominant with 8 samples testing positive for subtype H3. Four of the 8 positive sample were collected from ducks in live bird market in Surabaya, while the other 4 samples were collected from ducks in the live bird market in Sidoarjo Regency.

The phylogenetic tree of KPT Dk 21, WKR Dk 22, and WKR Dk 23 isolates in the HA gene indicates the viruses belongs to the H3 subtype (Fig. 3A). In addition,

Fig. 2. Representation of the distribution of sampling locations in this study (Created with https://app.datawrapper.de)

the phylogenetic analysis of KPT Dk 21, WKR Dk 22, WKR Dk 23, TMA Dk 11 and TMA Dk 13 isolates in Matrix gene indicates that the virus belongs to the subtype H3 (Fig. 3B). Our result shows that samples tested positive for influenza virus in this study are predominantly found in samples collected at the live bird market. In this study, surveillance was carried out on at least 16 live bird markets distributed across the provinces of Yogyakarta, Central Java, West Java, and East Java (Fig. 2). Most of the live bird markets in Indonesia are found close to slaughterhouses and meat sales. The sellers usually transport the various species of live poultry with pickup car or modified motorcycles with baskets from wood or bamboo from various regions in Indonesia and put the birds in one place mixed with other birds of various ages and various species (Fig. 4).

4 Discussion

The phylogenetic analysis showed that influenza virus belongs to subtype H3 influenza virus and become predominant virus found in this study. Influenza virus subtype H3 has a very diverse host range from birds to various mammalian species including pigs, horses, and dogs, and causes sporadic outbreaks in marine mammals [20]. After the emergence of the A/Hong Kong/1968 (H3N2) pandemic virus, it became endemic and caused annual seasonal epidemics in humans Domestic poultry in China has a lineage of influenza virus subtype H3 which causes mild to severe disease and has several subtypes such as H3N2, H3N3, H3N6 and H3N8, which have been isolated from domestic poultry globally. Experimental studies have also shown that the H3N8 subtype virus originating from poultry can replicate in the respiratory tract of mice, indicating that H3 isolates pose a threat of zoonotic infection [20]. Therefore, the H3 subtype virus poses a potential threat to animal and human health and poses a potential risk to public health. The possibility of reassortant events between the H3 subtype virus and the H5 subtype virus or other influenza virus subtypes, which could increase the adaptation and pathogenicity of the virus in humans, should be of concern. The genetic variation of AIV circulation in previous studies showed that the influenza viruses in Indonesia identified in 2003–2020 showed that the subtype H5N1 virus clade 2.1.3, clade 2.3.2,

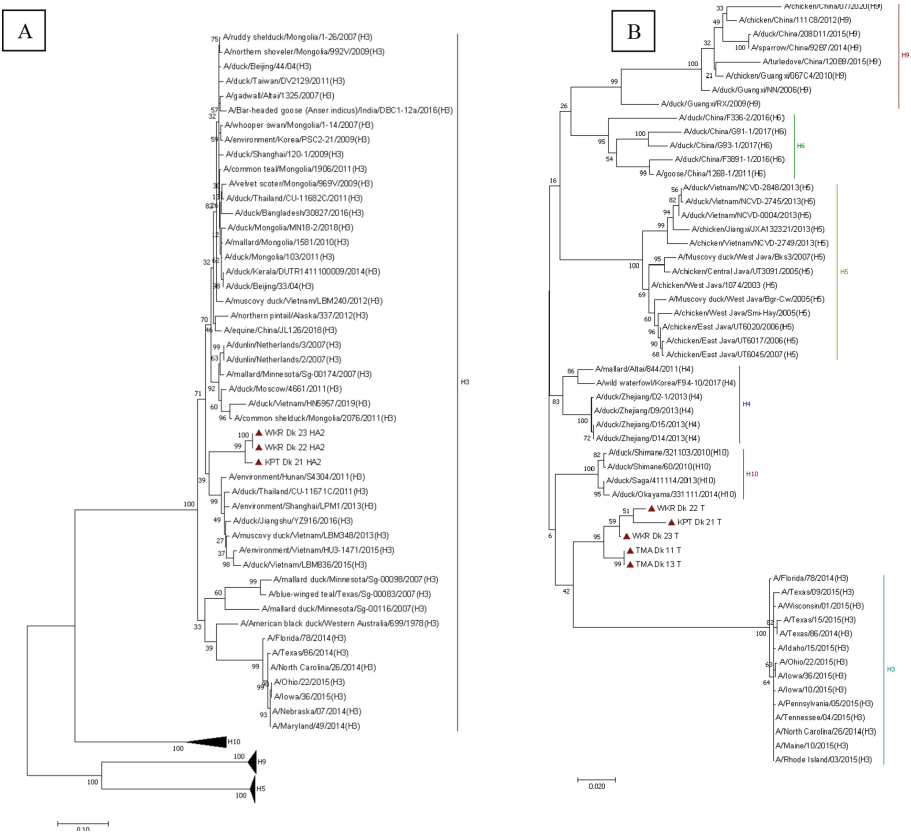

Fig. 3. The phylogenetic trees of HA (A) and MA (B) genes. The isolates in this study are shown with red triangle marks. HA: Hemagglutinin, MA: Matrix

subtype H9N2 and reassortant influenza viruses and other influenza virus subtypes were circulating in the live poultry market and farm in Indonesia. In 2019, co-circulation of HPAI-H5N1 clade 2.3.2.1c and LPAI-H9N2 were identified in duck farms during an AI outbreak in Yogyakarta province, Indonesia [21, 22]. Circulation of several viruses in the environment has the opportunity to cause co-infection and subsequently resulted in viral mutations (antigenic drift and antigenic shift), including reassortment events between the H5N1 virus and other influenza viruses including H3 subtype [23, 24]. In 2020, Dharmayanti et al. [9] reported that infection with the H9N2 reassortant virus that carrying the PB2 gene of the H5N1 virus caused a 10% mortality rate in chickens under laboratory conditions. The dynamics of avian flu viruses that undergo mutation, introduction and reassortant accompanied by the dominance of different viruses in the field cause surveillance as a control measure is needed to be able to anticipate changes in the phenotype, especially regarding its adaptation to humans.

AIV circulation does not only occur in poultry farms but also in traditional live poultry markets/live bird market. The live poultry market as a meeting point for humans and poultry has the potential become a source of the spread of AIV in poultry or even to

Fig. 4. Representation of the Indonesia live bird market condition in this study.

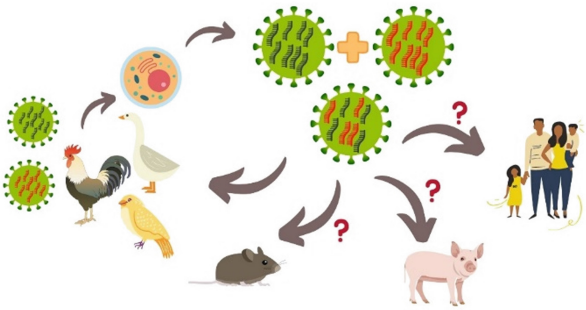

Fig. 5. Overview of the AIV co-infection process that produces novel viruses which may have the potential to cross the host barrier

other mammals and humans [25–27]. The live poultry market is a reservoir of AI virus and an ideal environment for genetic mixing and spread of AI virus since waterfowl as the reservoir of AIV is sold together with other poultry [28, 29]. The diversity of species and types of birds that are sold together in a live poultry market environment, such as various chickens, ducks, birds, and muscovy ducks can facilitate virus reassortment. (Fig. 5).

Dharmayati [8] in her study stated that the genetic diversity of the H5N1 virus in the live poultry market, in Indonesia, among them is the Reassortant H5N1 virus that occurs between clade 2.1.3 which has been circulating in Indonesia since 2003 and the new clade 2.3.2 which has been circulating since the end of 2012. The discovery of various influenza virus subtypes, particularly dominated by the H3 subtype in the live poultry market in this study indicates the necessity of alertness due to the

occurrence of mutations in these viruses that have the potential to be adapted to both mammalian and human hosts. Previously, a study reported the circulation of H3 and H10 viruses in Indonesia in which virus samples A/Chicken/Buleleng/BBVD488-9/2009 and A/Duck/Tabanan/BBVD573-10/2009 were AIV subtype H3 while sample code B4 (A/Chicken/Klungkung/BBVD006-1/2010) is an AIV subtype H10 [30]. H3 subtype AIVs can provide their gene segments to other HPAIVs and experience reassortment with other AIV subtypes. Therefore, the monitoring of H3 subtype AIVs and other AIVs subtype raised great concerns related to the zoonotic aspect of novel influenza variants [31].

5 Conclusion

The phylogenetic analysis showed that influenza virus belongs to subtype H3 influenza virus and become predominant virus found in this study. Influenza virus subtype H3 has a very diverse host range from birds to various mammalian species including pigs, horses, and dogs, and causes sporadic outbreaks in marine mammals. AIV circulation does not only occur in poultry farms but also in traditional live poultry markets/live bird market. The live poultry market as a meeting point for humans and poultry has the potential become a source of the spread of AIV in poultry or even to other mammals and humans. The discovery of various influenza virus subtypes, particularly dominated by the H3 subtype in the live poultry market in this study indicates the necessity of alertness due to the occurrence of mutations in these viruses that have the potential to be adapted to both mammalian and human hosts. In this study, the authors suggest that further research is needed to find out how the evolution and genetic relationship of the viruses found in this study with other viruses that circulating in Indonesia and other countries.

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