Influenza: Importance on Public Health and in other Species

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ABSTRACT

Influenza is a highly contagious disease that causes various outbreaks in different regions as a result of the interaction between humans and reservoirs. Due to its zoonotic and pandemic potential, this chapter reviews the importance of the disease in public health and in other species. We begin with understanding key aspects of its biology, genetic characteristics, structural and non-structural proteins, antigenic shifts and antigenic drift. Likewise, the ability of the virus to cross the barrier between species, its adaptation to the host and the migration and interaction of wild migratory waterfowl, as a natural reservoir of almost all subtypes of influenza type A, its dissemination, transmission and establishment will be addressed, in domestic birds and mammals. Subsequently, the emerging and re-emerging subtypes and lineages that caused outbreaks with different degrees of severity throughout human history are described. Finally, we summarize the diagnostic techniques applied, as well as the prevention and control measures. Although a century has passed after the most serious influenza pandemic, this disease continues to cause high rates of morbidity and mortality, mainly seasonally, and vaccination remains the most effective measure to control and prevent it. There is currently a global epidemiological surveillance system dedicated to the identification and characterization of the various antigenic variants circulating in different regions of the world. Therefore, it is important to continue monitoring its evolution and distribution, in addition to continuing to generate new diagnostic tools that, together with existing ones, lead us to a better determination of effective virus control strategies in human and animal populations.

Keywords: Influenza virus, public Health, surveillance, zoonotic, pandemic, reservoirs

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1. INTRODUCTION

Every day, the World Health Organization (WHO) and the World Organization for Animal Health (OIE-WOAH) report outbreaks of this disease in different regions. As a result of the interrelation between humans and reservoirs, it has given rise to the appearance of new subtypes and lineages, genetically and antigenically different from each other, which cause conditions in different degrees of severity depending on the host. Due to its zoonotic and pandemic potential recorded throughout history, society and governments from different countries have joined efforts to understand the infection dynamics of this disease.

2. INFLUENZA VIRUS OVERVIEW

The influenza virus is made up of four types, A, B, C and D. Type A influenza viruses (AIV, *Alphainfluenzavirus*) cause the greatest number of infections in humans and animals each year and have the potential to generate subtypes with pandemic potential. Types B and C (*Betainfluenzavirus* and *Gammainfluenzavirus*) mainly affect humans, although type C circulation has been reported in pigs and type D (*Deltainfluenzavirus*) also affects cattle, pigs, goats, and sheep (Long et al. 2019; Kuchipudi and Nissly 2018). These viruses belong to the family *Orthomixoviridae*, they can have a spherical or pleomorphic shape (~80-100 nm), they have a lipid envelope and their genome is made up of 8 segments of single-stranded RNA of negative polarity, which code for 10-17 proteins. Types C and D express 9 seven-segment proteins (Szewczyk et al. 2014; Hao et al. 2020; Skelton and Huber 2022). The complete genome contains about 14,000 nucleotides (Szewczyk et al. 2014). Each segment contains at least one open reading frame (ORF) that expresses a protein, and some segments may encode accessory proteins. Their names and functions are listed below in Table 1.

Two genes encode the viral envelope proteins haemagglutinin (HA) and neuraminidase (NA), which play crucial roles in the interaction between the virus and cellular receptors (Kuchipudi et al. 2021). Eighteen different antigenic subtypes of HA and eleven subtypes of NA have been described in the AIV. Each influenza virus contains, in any combination, only one HA subtype (H1-H18) and only one NA subtype (N1-N11), which can lead to a large number of possible subtypes, almost all of which are found in wild waterfowl, with the exception of subtypes H17N10 and H18N11 which have only been identified in bats (Tong et al. 2012; Tong et al. 2013; Kuchipudi et al. 2014; Puryear et al. 2016). The recognition of sialic acid receptor molecules on the surface of the host cell through the HA glycoprotein, leads to the initiation of the infection cycle with receptor-mediated endocytosis of the virus for the formation of an endosome, where the decrease of pH changes the structure of the HA and allows the fusion of the viral envelope and the endosome membrane, leading to the release of the viral segments into the cytosol (Dou et al. 2018). The viral segments are transported to the cell nucleus where their replication and transcription take place. Subsequently, the messenger RNAs (mRNA) are transported to the ribosomes to initiate the synthesis of viral proteins and form new vRNPs, as well as the proteins that make up the virus envelope and allow the generation of new viral progeny (Szewczyk et al. 2014; Zhu et al. 2022). Although AIVs lack the molecular mechanisms to repair errors that occur during their replication, this feature has allowed them to adapt genetically and antigenically, so that the existing strain can be replaced by a new variant. These continuous and permanent genetic changes are known as "drift" or "antigenic drift" (Webster and Govorkova 2014). Another feature of these viruses, which is of public concern, is their ability to exchange genetic material by recombination. This exchange process, known as "antigenic changes" or "shift", results in a new subtype different from that of both parent viruses. Due to this situation, the host lacks immunity to the new subtype and there is no vaccine that can confer protection. Historically, antigenic shift has resulted in highly fatal pandemics. For this to happen, the new subtype needs to have genes from influenza viruses of human origin that would make the infection easily

transmissible from person to person for a sustainable period of time (Webster and Hulse 2004; Webster and Govorkova 2014). The study of these pandemics has been of great interest; however, it is still not possible to predict those (Saunders-Hastings and Krewski 2016). Another key characteristic of influenza viruses that allows them to expand their genetic diversity is their ability to replicate in non-natural hosts, where the generation of these new variants that can reach pandemic potential can occur (Poole et al. 2014). For this, sialic acid (SA) receptors in the host cell play an important role in the evolution of these viruses. As previously mentioned, through the recognition of these receptors by the HA the infection cycle begins, and the differences in the structure of these glycoconjugates between species will determine the species-specific susceptibility to infection of the influenza virus (Kuchipudi et al. 2009; Long et al. 2019). AIV of avian origin bind preferentially to SAα2,3-Gal receptors, whereas viruses of human and porcine origin show preference to SAα2,6-Gal receptors. Therefore, those species that express both types of receptors, SAα2,3-Gal and SAα2,6-Gal, can be "mixing vessels" in which recombination of different subtypes of the AIV can occur (Kuchipudi et al. 2009; Nelli et al. 2010).

Table 1: Genes and proteins of influenza viruses.

Segment	Protein	Viral function
1	PB2[1]	RNA-dependent RNA polymerase complex (RDRP)
2	PB1[1]	RDRP complex
	PB1-F2[2,3]	Regulation of the immune response, apoptosis
	PB1-N-40[2,3]	Regulates expression of the PB1 protein
3	PA[1]	RDRP complex
	PA-X[2,3]	Degradation of messenger RNA, facilitates viral expression, and regulates the immune response
	PA-N155[2,3]	Unknown functions
	PA-N182[2,3]	Unknown functions
	P3[4]	RDRP complex
4	HA[1]	Recognition of host receptors and membrane fusion
	HEF[4]	Recognition of host receptors and membrane fusion, facilitates virion release and esterase activity
5	NP[1]	Packaging of the viral genome and assembly with the RDRP
6	NA[1]	Neuraminidase, facilitates the release of virions from the host cell
	NB[5]	Unknown function
	M1[4]	Packaging of the viral genome and assembly with the RDRP
	M2[4]	Ion channel, facilitates the release of virions
7	M1[3,5]	Packaging of the viral genome and assembly with the RDRP
	M2[3,5]	Forms the ion channel, facilitates the release of virions
	M42[1]	Forms the ion channel
	NS1[4]	Immune response evasion, interferon antagonist
	NS2[4]	Nuclear export protein for the synthesis of vRNPs
8	NS1[3,5]	Immune response evasion, interferon antagonist
	NS2/NEP[3,5]	Nuclear export protein for the synthesis of vRNPs

1: present in all four types of influenza viruses: A, B, C and D; 2: accessory protein; 3: present only in type A influenza viruses; 4: present only in influenza viruses type C and D; 5: present only in type B influenza viruses; 6: vRNPs: viral Ribonucleoprotein Complex

3. HOSTS

Wild migratory waterfowl such as ducks (*Anseriformes*), geese (*Passeriformes*), gulls and swallows (*Charadriformes*) are identified as the natural reservoir of almost all identified AIV subtypes, with the exception of bats, which are also natural reservoirs of some subtypes (García and Ramos 2006). This, together with the ability of the virus to cross the inter-species barrier, its adaptation to the host, and the

migration and interaction of these birds with other species, has favored its dissemination, transmission and establishment in domestic birds and land mammals, such as the human, pigs, horses, cattle, dogs, cats, and marine mammals, such as seals and whales, creating host-specific lineages in birds, humans, pigs and horses (Cauldwell et al. 2014; Kessler et al. 2021).

3.1. POULTRY

Avian influenza viruses (aAIV) cause serious economic losses in poultry. According to the severity in the clinical presentation of the virus, strains with two forms of presentation have been identified, in low pathogenicity viruses (LPAIVs) a mild clinical picture is observed, compared to highly pathogenicity viruses (HPAIVs), that result in death in two or three days, due to the severity of the clinical picture (Jeong et al. 2009). This will depend on the species, type of bird, and age, as well as the various environmental conditions in which they occur. Clinical signs caused by HPAIVs can range from sudden death with no obvious clinical signs to variable clinical presentations, including respiratory signs, such as ocular and nasal discharge, cough, dyspnea, decreased vocalization, marked reduction in food intake and water, cyanosis of the skin devoid of feathers, wattles and comb, incoordination and diarrhea (Swayne et al. 2020). High morbidity is usually accompanied by inexplicably high and rapidly increasing mortality. The LPAIVs viral strains commonly affect chickens, turkeys, and other birds of economic importance, and are associated with the H5 and H7 subtypes, causing respiratory diseases, reducing egg production, and low mortality (Cox et al. 2017; WOAH, 2022). Low virulence viruses can mutate to highly virulent strains after circulating for (sometimes short) periods in a poultry population. For example, during a 1983-1984 epizootic in the United States of America, the H5N2 virus initially caused low mortality, but within six months it became highly virulent, with approximately 90% mortality. Control of the outbreak required the destruction of more than 17 million birds at an approximate cost of $65 million dollars. In Italy (1999-2001) due to the H7N1 virus initially had low virulence and later transformed into a highly virulent form within 9 months. More than 13 million birds died or were culled (Monne et al. 2014). aAIVs are also a concern for public health due to the fact that sporadic cases have been identified in the human population, mainly of the H5, H7 and H9 subtypes, as well as the generation of possible pandemics in the event of additional mutations that favor sustained person-to-person transmission, such as the infection caused by an Eurasian lineage HPAI H5N1 with a case fatality rate greater than 50% (Nelli et al. 2012; Cox et al. 2017).

3.2. PIGS

Currently, the disease is widely distributed in all pig-producing countries, where China is the world leader (Borkenhagen et al. 2019). The H1N1, H1N2 and H3N2 subtypes of influenza viruses are the most frequently reported worldwide, with H1N1 being the most widely disseminated (Zell et al. 2013). However, the origins and the genetic and antigenic characteristics of these viruses differ depending on the continent or region in which they are isolated, due to both the phenomenon of recombination and genetic drift (Nelson and Vincent 2015). These differences are especially evident in the case of the H1N1 subtype, the virus present in America (classical swine) originated directly from the H1N1 that caused the "Spanish influenza" of the year 1918 (Kessler et al. 2021), while the Eurasian H1N1 has an avian origin and was first isolated in the late 1970s in Italy. Both viruses have different genetic and antigenic characteristics (Van Reeth and Vincent 2019). In the case of the H3N2 subtype, it is a triple recombinant that is characterized by containing the genes that code for HA and NA of human origin, while the genes belonging to the internal viral proteins are of avian origin in the European strain (Ruiz-Fons 2017), and are of avian and porcine origin in the case of the North American subtype (Nelson and Vincent 2015). Finally, the H1N2 subtype, isolated in Europe in 1994 (Brown et al. 1995),

is a recombinant that contains all the genes of porcine H3N2 with the exception of the HA gene, which comes from an H1N1 of human origin. However, in some countries, H1N2 has been detected with HA of avian origin, as is the case in Denmark and France (Hjulsager et al. 2006; Kyriakis et al. 2011). Other influenza virus subtypes have also been isolated, although less frequently and have not become widely established in the swine population. These include the H1N7, H4N6, H3N3 and H3N1 subtypes (Brown et al. 1994; Karasin et al. 2000, 2004; Lekcharoensuk et al. 2006). The swine influenza virus has been found primarily in pigs, but has also been found in humans, turkeys, ducks and dogs (Ma et al. 2015, 2017). It has been associated with the 1918 (H1N1), 1957 (H2N2), 1968 (H3N2) and 2009 (H1N1) pandemics (Easterday, 2003; Crosby, 2003; Krueger and Gray, 2012; Mena et al. 2016; Taubenberger et al. 2019). The global transport of infected animals has also been implicated in the movement of various virus strains across countries and continents. In China, there are viruses of North American and Eurasian lineages co-circulating, suggesting that international trade and agricultural fairs may have facilitated the introduction of these viruses (Bowman et al. 2014, 2017; Duwell et al. 2018; Schicker, 2016; Gray et al. 2012; Trovão and Nelson 2020).

4. OTHER HOSTS

4.1. HORSES

This species is mainly affected by the A/H3N8 subtype, severely affecting the respiratory tract, with a fatality rate of 20%, in unvaccinated animals (Sack et al. 2017; Singh et al. 2018). Various epidemic outbreaks have been registered, which caused great economic losses to the affected countries, mainly in meat production and in the racing industry, as it was in Mongolia and Australia (Cowled et al. 2009; Sack et al. 2017). Various studies have shown the ability of these viruses to produce clinical and subclinical infections in horses and humans, and possibly in dogs and cats (Borkenhagen et al. 2019; Sack et al. 2019). Through an archaeo-immunological study, it was possible to detect neutralizing antibodies against the A/Equino-2/63 virus in individuals born in 1870 and 1900 (Chambers 2022). Although various data have been reported evidencing human exposure to these viruses, the risk of infection is low (Larson et al. 2015; Xie et al. 2016).

4.2. DOGS

In recent years, a high susceptibility of dogs to influenza virus infections has been frequently observed, mainly in those that are found in places with a high population density such as shelters, races or kennels (Voorhees et al. 2018). This species has been affected by the H3N8 subtype of the equine influenza virus in 1999, as well as by an avian type H3N2 virus in 2005 or 2006, among others (H1N1, H5N1, H6N1, H9N2) (Parrish et al. 2015; Jang et al. 2017; Sun et al. 2013; Songserm et al. 2006; Lin et al. 2015). Although dogs have been shown to be susceptible to infection with influenza viruses of human origin, there have been no documented cases of canine influenza virus infections in humans or in personnel assigned to work in places such as shelters or kennels (Chen et al. 2018; Krueger et al. 2014).

4.3. CATS

Reports of infection with the influenza virus in this species have been documented since 2004; its susceptibility to infection with viruses of human, avian, canine and equine origin has been demonstrated (Borkenhagen et al. 2019). Infection with the pandemic A/H1N1 virus was observed in Italy in 2011, and during 2016-2017, more than 500 shelter cats were infected with the H7N2 subtype in New York, USA

(Fiorentini et al. 2011, Hatta et al. 2018). The veterinarian who treated the infected cats developed symptoms and A/H7N2 virus infection was confirmed (Lee et al. 2016). An employee from another shelter was also confirmed to have the same subtype by serological testing (Poirot et al. 2018).

4.5. BATS

The H17N10 and H18N11 subtypes of influenza A virus have been identified in fruit bats, respectively, in the yellow-shouldered bat (*Stunira lilium*) in Guatemala, and in the flat-faced fruit bat (*Artibeus planirostris*) in Peru. In addition, serological studies have shown a high seroprevalence among bat populations from Central and South America. The little brown bat may be a source of new genetic variants, due to the co-expression of receptors that recognize avian and human-type viruses (Tong et al. 2012; Tong et al. 2013; Chothe et al. 2017).

5. EMERGING AND RE-EMERGING VIRUSES

Various pandemics caused by influenza viruses have been reported throughout human history. The first, in 1580, identified as “wind sickness” due to its rapid spread, originated in Asia, spread to Europe, Africa, and the American continent through trade routes (Rafeek et al. 2017). There are records of approximately thirty-one subsequent events, including three that occurred in the last century, in 1918-19, 1957 and 1968, and six in the 19th century: 1800-1801, 1837, 1843, 1857, 1874, and in 1889-92 (Miller et al. 2009; Tognotti, 2009). The most severe of the pandemics on record was the Spanish flu. Various scientists estimate that it caused 40-50 million deaths. The disease spread through North America, Europe, Asia, Africa, Brazil, and the South Pacific. According to the molecular analyzes carried out on the tissues of the 1918 victims, the RNA fragments detected suggest that it was a virus with an A/H1N1 avian-human rearrangement introduced into the population approximately 6 months before the start of the pandemic (Taubenberger et al. 2019). Subsequently, two less severe pandemics originated in Asia but spread throughout the world. In 1957, the “Asian flu” occurred in China, which spread rapidly, replacing the circulating A/H1N1 with A/H2N2. Likewise, in Hong Kong, in 1968, an A/H3N2 virus emerged that spread throughout the world until 1969, and in 1976-1977 the A/H1N1 subtype reemerged (Kilbourne, 2006). In 1997, a highly pathogenic A/H5N1 virus of avian origin acquired human infectivity in Hong Kong; from 1999 to 2003, in Italy, seroconversion of individuals who were in contact with birds infected with A/H7N1 and A/H7N2 viruses was demonstrated, and in Japan, infection and seroconversion of workers in production units affected by the low pathogenic A/H5N2 virus were described (Campitelli et al. 2004; Puzelli et al. 2005; García and Ramos 2006; Tognotti, 2009). Other subtypes of avian origin have also affected humans such as A/H9N2 in China, A/H7N7 in the Netherlands, and A/H7N3 in Canada (Stegeman et al. 2004; Hirst et al. 2004; Kemink et al. 2004; Tweed et al. 2004; Gu et al. 2017). The most recent influenza pandemic recorded originated in Mexico in April 2009 due to a triple recombinant A/H1N1 virus (porcine-avian-human), and in August 2009 it was declared by the WHO as the first pandemic of the XXI century (Franco-Paredes et al. 2009). The main subtypes identified as candidates to generate a pandemic are: A/H5Nx, AH7N9, A/H9N2 and A/H10Nx (Sutton, 2018; Taubenberger et al. 2019). For this reason, WHO has developed tools for risk analysis (WHO, TIPRA) (Global influenza Programme WEP, 2020) as well as the Center for Disease Control and Prevention (CDC, IRAT) (Centers for Disease Control and Prevention, 2020). These programs analyze the phenotypic properties of the virus (specific recognition receptors, transmission between species, etc.), characteristics of the susceptible population (signology, immune response, etc.), the ecology of the virus, and its epidemiology in non-human hosts.

6. DIAGNOSIS

Due to its importance in public health, early and opportune diagnosis should be considered. In typical flare-ups, a provisional diagnosis can be made based on clinical and pathologic findings. But it must be confirmed by virus isolation or by detection of its specific antibodies. The virus can be isolated from nasal secretions during the febrile phase or from lung tissue (3 to 5 days) during the early acute stage (Torremorell et al. 2012). The isolation is done by inoculation in the chorioallantoic membrane of a chicken embryo of 9-11 days, free of specific pathogens (SPF). The virus isolation technique is considered the standard for virus detection through which the viability and infectivity of the virus can be determined, information that cannot be obtained with molecular amplification and antigen detection techniques. For its detection, the specific hemagglutination technique is used (Van Reeth and Vincent 2019; Ravina et al. 2020). Another option is to use the *Madin Darby Canine Kidney* (MDCK) cell line for influenza isolation (Ravina et al. 2020). A retrospective diagnosis can be made, starting from serum samples taken during the acute and convalescent stages of the disease, demonstrating the presence of specific antibodies, using the hemagglutination inhibition test. It is one of the most widely used tests in countries where the disease is endemic, since it recognizes HA that is specific for each subtype and does not present cross-reactions (Truelove et al. 2016). Other methods to detect the virus, viral antigen, or specific antibodies are direct and indirect immunofluorescence techniques. It is frequently used for the diagnosis of influenza in humans. It can be used both in clinical samples and in cell cultures. There are other tests such as neuraminidase inhibition, viral seroneutralization, and ELISA (Jin et al. 2004; Woolcock and Cardona 2005; WHO, 2005). The high similarity of the pandemic H1N1/2009 virus to other H1N1 of porcine origin made viral identification highly dependent on nucleic acid sequencing. Currently, in addition to the CDC protocol for specific diagnosis by real-time RT-PCR recommended at the very beginning of the H1N1/2009 pandemic, laboratories in various countries have refined the specificity of this assay and various protocols. The real-time RT-PCR technique from nasal swabs has been the commonly used method for the detection of type A influenza viruses as part of surveillance (Ellis et al. 2009), and it is based on the detection of the matrix gene (M), a highly conserved region of influenza A viruses, so that it allows the detection and quantification of practically all influenza viruses (Spackman and Suarez 2008; Slomka et al. 2010). In addition, other RT-PCRs (conventional and real-time) are capable of amplifying porcine (H1, H3, N1 and N2) and avian (H5 and H7) haemagglutinins and neuraminidases (Lee et al. 2008; Mallinga et al. 2010; Shi et al. 2014; Lee et al. 2021). Another test that is used, and that has been widely accepted, is the One-Step-Real-Time-Multiplex RT-PCR, which has already proven to be fast, sensitive, and specific when applied during H5N1 influenza outbreaks (Payungporn et al. 2006).

7. PREVENTION AND CONTROL

A century after the most severe influenza pandemic, this disease continues to cause high morbidity and mortality rates, mainly during the winter, and vaccination continues to be the most effective measure to control and prevent it. Today, there is a global epidemiological surveillance system dedicated to the identification and characterization of the various antigenic variants circulating in different regions of the world (Holloway et al. 2014; Hay and McCauley 2018). The CDC, in Atlanta, Georgia, in the United States, houses the WHO Center for Disease Surveillance. Led by health professionals dedicated to analyzing the annual reports of morbidity and mortality caused by the different circulating strains, they recommend which strains should be included in the preparation of vaccines for the following winter season in the northern and southern hemispheres (Malik et al. 2020). Vaccines can significantly reduce the incidence of infection with the influenza virus and other medical complications (Bosaeed and Kumar 2018).

Inactivated vaccines, split-virion vaccines, subunit vaccines, virosome vaccines, live-attenuated vaccines, and recombinant vaccines are available (Rajao and Pérez 2018). Another way to mitigate the effects of this disease is through the use of antivirals, which are classified as those that block the ion channel (M2) of the virus, and also neuraminidase (NA) inhibitors (Schnell and Chou 2008; Gubareva et al. 2010; Ison et al. 2017). Unfortunately, various studies and results on practice have shown the development of resistance against this therapeutics, in addition to the high cost of treatment, which ranges between 30 and 70 dollars a day for 10-15 days. The main preventive action that can help limit the spread of the virus in the human population is to avoid as far as possible contact with sick people; but in the case of sick people, they should stay at home for at least 24 hours after initiation of the classic symptoms (cough, runny nose, muscle pain, fever, among others), cover nose and mouth, clean and disinfect surfaces and wash hands frequently, avoiding touching the mouth, nose and eyes (Lancet 2018). Biosecurity practices and vaccination are preventive measures that minimize the transmission of influenza virus in pigs and from pigs to other species. Other prevention measures are: applying a quarantine period to newly introduced animals, avoiding contact with wild birds, limiting and/or excluding movements of people, such as the use of clothing and boots exclusive to the production unit, having a control in the access of personnel or restrict the entrance to visitors, limit the entrance of sick personnel, the obligation to shower before the entrance and exit of any person who has access to the production unit, have a personnel vaccinated against influenza, restrict access to animals and vehicles from other production units, establish adequate cleaning, and disinfection methods for all areas including vehicle entrances (CDC, 2012; Van Reeth and Vincent 2019). The application of therapeutic treatment in animals is unaffordable. The application of antibiotics is common but only to prevent the presentation of secondary infections, these are added to water. Expectorants and antipyretics are also used (Van Reeth and Vincent 2019). Knowledge of the serological status is essential, since depending on this we will decide both the application and change of a vaccination protocol (Salvesen and Whitelaw, 2021). Knowing well the dynamics of the influenza virus in the population can help in the determination of effective strategies for the elimination of the virus (Torremorell et al. 2012).

8. CONCLUSIONS

Worldwide, outbreaks caused by influenza viruses cause great economic losses. Therefore, it is extremely important to continue with active epidemiological surveillance throughout the world, monitoring its evolution and distribution, in addition to continuing to generate new diagnostic tools that, together with the existing ones, lead to better control of the virus in human populations and animals.

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