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REVIEW

Quantitative measurement of influenza virus transmission in animal model: an overview of current state

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Abstract

Influenza virus transmission is a crucial factor in understanding the spread of the virus within populations and developing effective control strategies. Studying the transmission patterns of influenza virus allows for better risk assessment and prediction of disease outbreaks. By monitoring the spread of the virus and identifying high-risk populations and geographic areas, it is possible to allocate resources more effectively, implement timely interventions, and provide targeted healthcare interventions to diminish the burden of influenza virus on vulnerable populations. Theoretical models of virus transmission are used to study and simulate of influenza virus spread within populations. These models aim to capture the complex dynamics of transmission, including factors such as population size, contact patterns, infectiousness, and susceptibility. Animal models serve as valuable tools for studying the dynamics of influenza virus transmission. This article presents a brief overview of existing research on the qualitative and quantitative study of influenza virus transmission in animal models. We discuss the methodologies employed, key insights gained from these studies, and their relevance.

Keywords Influenza virus · Transmission · Animal models · Quantitative measurement · Direct contact · Respiratory droplets · Airborne transmission

Introduction

The influenza virus poses a serious threat to public health worldwide due to potential to cause epidemics and pandemics. The incidence and mortality from influenza virus remain a significant problem for humanity, despite continuous monitoring and improvement of the healthcare system. Every year, 3 to 5 million people are infected with the influenza virus, with estimates ranging from 290,000 to 650,000 fatalities (Kim et al. 2022).

Transmissibility refers to the properties of virus and is defined as the probability of infecting a healthy organism upon contact with an infected one (Jones 2007). The pathogens infectiousness, the contagiousness of the infected organism, the susceptibility of the recipient organism, and the environmental factors all have a role in how transmissible an infection is. There are various models for assessing transmissibility, primarily based on the reproduction number R_0, which is defined as the number of organisms that will be infected by an infected individual introduced into a fully non-immunized environment in the absence of specific epidemiological measures aimed at preventing the spread of the disease. R_0, in turn, is also evaluated using mathematical models. For example, Smith et al. estimated R_0 for malaria based on a study of an African population (Smith et al. 2007). In the work of Guerra et al., median R_0 values for measles were calculated based on a systematic review of databases (Guerra et al. 2017).

Similar approaches can be applied to other respiratory agents as well. As a respiratory virus, influenza can be transmitted through direct (physical) contact, indirect contact (via fomites), and airborne droplets. Constant antigenic changes of the influenza virus can lead to the emergence of strains with high epidemic and pandemic potential. The Tool for Influenza Pandemic Risk Assessment (TIPRA) was created by WHO to provide a transparent and uniform method to facilitate the assessment of the risk associated with influenza viruses with the potential to cause a pandemic. One of the assessed risk elements is transmission in animal models by different infection routes. Understanding how to properly assess the transmission

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of the influenza virus in animal models will enable the control of emerging strains with epidemic and pandemic potential. Studying virus transmission in animal models allows for controlled experiments that provide insights into the factors influencing transmission dynamics, including contact patterns, environmental conditions, and host characteristics.

There is a sufficient amount of research and reviews on the transmissibility properties of the influenza virus in various animal models, but there are fewer studies specifically dedicated to quantitative measurement of transmissibility. It can be explained by several reasons. First of all, conducting controlled studies to measure influenza transmission in animals may raise ethical concerns. Animals used in research must be treated humanely, and there are stringent regulations and guidelines in place to ensure their welfare. This can make it challenging to design and conduct studies that involve intentional exposure to infectious agents like the influenza virus. Also, there are species-specific factors and methodological challenges. Influenza virus exhibits species-specific characteristics, meaning it has different interactions and effects in different animal species. Animal models often differ from humans in terms of anatomy, immune response, and receptor distribution, making it difficult to extrapolate findings directly to humans. Additionally, accurately quantifying transmission requires careful experimental design, control groups, and statistical analysis, which can be complex and resource-intensive. Consequently, studying influenza transmission in animals may not always provide direct insights into human transmission dynamics. Finally, there are public health priorities. Research efforts have historically focused on developing vaccines, antiviral medications, and understanding human transmission dynamics to guide public health interventions. These priorities may limit the resources available for conducting extensive quantitative studies of influenza transmission in animals.

One of the most important stages for successful infection is the binding of viral particles to susceptible cells surface receptors. For the influenza virus, these receptors are sialic acid residues on the cells of the respiratory or gastrointestinal epithelium, depending on the host species. Avian influenza viruses primarily bind to α2,3-linked sialic acids, while human strains bind to α2,6-linked sialic acids (Gambaryan et al. 2002; Shinya et al. 2006). The presence and distribution of such receptors are the key criteria for an organism susceptibility to influenza virus infection.

Theoretical models of respiratory virus transmission

Theoretical models of respiratory virus transmission play a crucial role in understanding the dynamics of how these viruses spread within populations. These models employ mathematical and computational frameworks to simulate and predict the transmission patterns, assess the impact of different factors, and inform public health interventions. By integrating epidemiological principles, population dynamics, and specific virus characteristics, these models aid in predicting the impact of interventions, assessing the effectiveness of different control measures, and exploring scenarios for disease containment. There are different types of theoretical models used in the study of respiratory virus transmission:

1. Compartmental models. Compartmental models split the population into several compartments according on how infected they are (Tillett 1992). The most commonly used compartmental model for respiratory virus transmission, including influenza virus, is the susceptible-exposed-infectious-recovered (SEIR) model (Gilbert et al. 2014; Etbaigha et al. 2018; Rezapour and Mohammadi 2020). This model tracks the flow of individuals between compartments and incorporates parameters such as infection rates, incubation periods, and recovery rates. SEIR models can be expanded to include more detailed sub-compartments and variations, such as age-specific compartments or spatial considerations.
2. Agent-based models. Agent-based models represent individuals as discrete agents and simulate their interactions within a population (Eubank et al. 2004). Each agent possesses specific attributes and behaviors that influence their susceptibility, infectiousness, and movement patterns. Agent-based models allow for the incorporation of individual-level heterogeneity, contact networks, and spatial information. These models can provide insights into the impact of behavioral factors, contact patterns, interventions on transmission dynamics and can be applicable to the influenza virus (Arduin et al. 2017; Krauland et al. 2023).
3. Network models. Network models represent individuals as nodes in a network and interactions as edges between nodes (Keeling et al. 2011). These models capture the structure of social or contact networks and allow for the study of disease transmission dynamics within the network framework. Network models can reveal the role of influential individuals (e.g., super-spreaders) or identify key connections for targeted interventions. They also examine the impact of network structure on the spread of respiratory viruses, including influenza virus (Jin et al. 2011; Xu and Wu 2021).
4. Spatial models. Spatial models incorporate the geographical dimension to study how respiratory viruses spread across different locations or regions (Tatem et al. 2012). These models consider the movement of individuals, the spatial distribution of the population, and factors that affect transmission within specific areas. Spatial

models help understand the local and global patterns of virus transmission, the effect of travel on disease spread, and the impact of interventions in different geographical contexts. Such models are useful for evaluation of transmission risk and prediction of hotspots of novel virus (Nelson et al. 2011; Prosser et al. 2013).

5. Stochastic models. Stochastic models incorporate randomness and probability in the modeling framework (Keeling and Rohani 2011). These models consider the inherent variability and uncertainty associated with disease transmission. Stochastic models account for the probabilistic nature of events such as infection, recovery, and contact, allowing for the assessment of uncertainty and the estimation of confidence intervals around model predictions. It also applies to influenza virus spread (Baleanu et al. 2019; Whitmanid and Jayaprakash 2020).

Quantitative transmission models of influenza virus

Quantitative measurement of influenza virus transmission in animals involves assessing the efficiency and dynamics of virus spread within a population. Such parameters are crucial for the implementation of effective control measures. There are several methods and approaches used to quantitatively measure influenza virus transmission in animal populations:

1. Direct contact transmission studies. In this approach, susceptible to influenza virus infection animals are placed in direct contact with infected ones. Transmission rates can be quantified by monitoring the infection status of the susceptible animals over time. Quantitative measurements involve monitoring infection rates, transmission efficiency, and the impact of factors like viral load, host immune responses, and viral shedding.
2. Respiratory droplet transmission studies. Influenza viruses are primarily transmitted through respiratory droplets. It is possible to simulate this mode of transmission by using specialized equipment to generate aerosols containing virus particles. These aerosols are then exposed to susceptible animals, and transmission rates can be determined by monitoring the infection outcomes. Quantitative measurements include assessing the dose–response relationship, infectiousness of emitted droplets, and the effectiveness of interventions such as masks or air filtration systems.
3. Airborne transmission studies. In addition to respiratory droplets, influenza viruses can also be transmitted through the air over longer distances. To simulate such conditions specialized chambers or cages to house infected and susceptible animals separately but connected by airflow are used. By monitoring virus transmission in this controlled environment, it is possible to quantify the efficiency of airborne transmission. Quantitative measurements are the same as for airborne transmission.
4. Serial passage studies. This method involves serially infecting animals with influenza virus and then transferring the virus from infected animals to new hosts. Repeating this process over multiple generations allows to determine the transmission potential of the virus and assess changes in transmissibility over time. Quantitative measurements can include determining transmission rates, genetic changes in the virus, and evaluating the impact of mutations on transmission efficiency.
5. Mathematical modeling. Mathematical models are extensively used for simulation and prediction of influenza virus spread in animal populations. These models incorporate various factors, such as contact rates, transmission probabilities, and population demographics, to estimate the transmissibility of the virus. The model outputs allow to quantify transmission dynamics and assess the impact of different environmental factors.

Animal models

Various animal models are used to study influenza virus transmission, including mice, ferrets, guinea pigs, hamsters, non-human primates and etc. Each model has its advantages and limitations. Below is a brief overview of the most commonly used animal models.

1. **Mouse Model**

Among the animal models for influenza virus study, mice (*Mus musculus*) are one of the most commonly used models due to their ease of manipulation and low cost of purchase and maintenance. Although mice are not natural hosts of the influenza virus, they exhibit some disease symptoms upon infection, and high titers of the influenza virus RNA are detected in homogenates of internal organs. Typically, clinical signs appear 2–3 days after infection, and severity depends on the dose. Clinical manifestations include lethargy, huddling, ruffled fur, weight loss, hypothermia, cyanosis, occasional neurological disorders, cytokine storm, primary viral pneumonia, and death (Barnard 2009; Tripp and Tompkins 2009; Margine and Krammer 2014). Seroconversion, as in humans, is observed approximately 21 days after infection/vaccination (Bharmoria et al. 2016). Despite the advantages of mouse model for studying the influenza virus, studying transmissibility in mice is challenging. Mice can transmit influenza virus through direct contact that occurs through close physical

proximity and can involve various routes, including nasal secretions, saliva, and feces (Bao et al. 2014). Also, it can be transmitted through respiratory droplets expelled during coughing, sneezing, or breathing. The efficiency of transmission can vary depending on factors such as the strain of the virus and the specific mouse model being used. There are few available studies in which transmission of the influenza virus was observed in mice (Eaton 1940; Schulman and Kilbourne 1962; Schulman 1968). These studies have shown that effective transmission requires prior adaptation of strains, and only certain strains adapt with good efficiency. Additionally, specific laboratory conditions such as airflow rate, humidity, and temperature are crucial for efficient transmission. More recent studies also indicate that influenza virus transmission in mice is inefficient and often requires direct contact, adherence to the aforementioned conditions, or the use of humanized mice (Lowen et al. 2006; Edenborough et al. 2012; Ortigoza et al. 2018; Mendoza et al. 2020). This situation can be explained by the absence or insufficient presence of α2,6 receptors on the surface of mouse epithelial cells, making it difficult to infect them with human strains of the influenza virus (Ibricevic et al. 2006).

2. Ferret Model

Ferrets (*Mustela putorius furo*) are considered the most suitable animal model for transmissibility studying. Due to their ability to adapt to infection, similar clinical sights, and pathogenesis, ferrets closely mimic human influenza infection. Clinical signs include sneezing, nasal secretions, lethargy, hyperthermia, and weight loss. Some of the influenza virus strains in ferrets can lead to pneumonia, tracheobronchitis, and, in severe cases, death (Smith and Sweet 1988). The acute phase of illness for influenza in ferrets typically lasts for 3–5 days. During this period, the animals are highly contagious and can transmit the infection. The distribution of receptors in ferrets is similar to humans, their respiratory tissues express both α2,3- and α2,6-linked sialic acids (Jia et al. 2014). It makes ferrets an excellent model for studying of influenza virus transmission. Limitations of the model include the high cost of acquisition and maintenance and limited availability of specific immunological reagents. Similar to humans, influenza in ferrets primarily affects the epithelium of the upper respiratory tract, but there is also a possibility of lower respiratory tract infection (Huang et al. 2014; Camp et al. 2015). Ferrets can transmit influenza through direct contact, including close physical proximity, such as snout-to-snout contact or fighting by exchange of nasal secretions and saliva (Zhu et al. 2013). Ferrets are capable of generating and expelling respiratory droplets containing infectious virus particles and also can transmit influenza viruses through airborne routes (Richard et al. 2020). Susceptible ferrets can acquire the infection by inhaling these droplets or through contact with contaminated surfaces. For example, it was demonstrated that influenza virus transmission between ferrets could occur via small particle aerosols, simulating airborne transmission (Lowen et al. 2007). There are several quantitative studies of influenza virus transmission using ferrets as animal model. Some quantitative data were obtained by serial passage studies on ferrets (Sutton et al. 2022). The indicators for influenza A virus transmissibility in ferrets were estimated in airborne transmission (Pulit-Penaloza et al. 2023). One of the recent studies proposed a quantitative model of airborne transmission of influenza virus in ferret model (Gudymo et al. 2023).

3. Guinea Pig Model

Guinea pigs (*Cavia porcellus*) are widely used for studying influenza virus transmission due to certain similarities they share with humans in terms of respiratory physiology and susceptibility to non-adapted strains of the influenza virus. They have smaller sizes, making them commercially more advantageous than ferrets. Anatomically and physiologically, the lungs of guinea pigs are more similar to humans than the lungs of rats and mice (Ressmeyer et al. 2006). Nasopharyngeal swabs of infected guinea pigs contain influenza virus RNA, and seroconversion is observed after infection. In some cases, signs of viral pneumonia have been detected during necropsy (Tang and Chong 2009; Kwon et al. 2009). However, the most significant disadvantage of the guinea pig model is the absence of significant clinical symptoms of the disease. Increased mucus secretion from the nose and mild sneezing can be considered relative indicators of infection (Steel et al. 2009). The guinea pig respiratory tract has both α2,3 and α2,6 sialic receptors, which are presented in the nasal tract and the trachea, while in the lungs predominantly contain α2,3 receptors (Sun et al. 2010). Therefore, guinea pigs are generally susceptible to a wide range of influenza virus strains, including both human and avian origin viruses. Guinea pigs, like humans, primarily transmit influenza viruses through respiratory droplets (Lowen et al. 2006). In addition to respiratory droplet transmission, studies have shown that influenza viruses can be transmitted through direct contact between infected and susceptible guinea pigs (Bouvier et al. 2008; Pica et al. 2012). Some studies have suggested the possibility of airborne transmission of influenza viruses in guinea pigs (Mubareka et al. 2009; Asadi et al. 2020). Due to influenza virus susceptibility, it is possible to investigate quantitative parameters of transmission on guinea pigs such as infectivity, magnitude of replication, kinetics of replication, efficiency of transmission, and kinetics of transmission (Danzy et al. 2021).

4. Hamster Model

Hamsters (*Mesocricetus auratus*) can also be used to study the properties of the influenza virus. They are cheap and easy to handle, susceptible to influenza, and can be used for transmissibility studies and vaccine effectiveness assessments. The main disadvantage of the hamster model is the absence of clinical signs of the disease. Like most mammals, viral infection in hamsters primarily affects the upper respiratory tract, which is confirmed by the presence of a high titer of the virus in nasopharyngeal swabs (Ali et al. 1982). Additional sigh of infection is a specific immune response (Taylor and Parodi 1942). The distribution of sialic acid receptors is very similar to the human respiratory tract (Iwatsuki-Horimoto et al. 2018). Influenza virus can be transmitted between hamsters through direct contact. It has been observed for both human and avian influenza strains (Belser et al. 2013). Influenza viruses can also spread through the air and infect susceptible hamsters in close proximity (Herfst et al. 2012). In addition to direct contact and airborne transmission, influenza viruses can persist on surfaces (fomites) for a certain period. Hamsters can get infected by coming into contact with virus-contaminated objects such as bedding, cages, or water bottles (Bouvier and Lowen 2010). Respiratory droplets, larger than aerosols, are another mode of influenza virus transmission on hamsters. These droplets can be generated when an infected hamster exhales, coughs, or sneezes, and can transmit the virus to susceptible hamsters in close proximity (Imai et al. 2012). Despite the susceptibility of hamsters to the influenza virus and the possibility of transmission, the absence of clinical signs makes the hamster model not extensively used. Therefore, there are no research devoted to the for the purpose of quantitative study.

5. Chicken Model

Chicken (*Gallus gallus domesticus*) is a suitable model for the study of avian strains of the influenza virus transmission, since the epithelium of the lower digestive tract contains a large number of α2,3 receptors (Cui et al. 2017; Bertran et al. 2017). Symptoms of infection include cough, nasal discharge, respiratory distress, diarrhea, cyanosis, and paralysis (Hemmink et al. 2018). There are a few quantitative studies of influenza virus transmission. For example, the transmission rate of avian influenza virus from experimentally infected chicken to naïve ones was investigate (Takadate et al. 2023). The main disadvantage of chicken model is the impossibility of studying human strains of the influenza virus, due to the lack of α2,6 receptors.

6. Swine Model

Transmission of influenza virus in pigs (*Sus scrofa*) extensively studied due to the important role of pigs as intermediate hosts for the generation of novel influenza viruses with pandemic potential. Pigs can serve as a mixing vessel for the reassortment of influenza viruses. Due to the presence of both avian and human receptor types in their respiratory tract, pigs can be infected with influenza viruses from avian and mammalian sources (Ito et al. 1998; Suzuki et al. 2000). This provides an opportunity for genetic reassortment between different strains, potentially leading to the emergence of novel viruses. Influenza viruses can be transmitted directly between pigs through close contact (Lange et al. 2009). Infected pigs shed the virus through respiratory secretions, and healthy pigs can become infected by inhaling the virus or through contact with contaminated surfaces or objects. Influenza viruses can also be transmitted between pigs through aerosols, when infected pigs release virus-containing droplets into the air through coughing or sneezing, and susceptible pigs can become infected by inhaling these infectious aerosols (Zhang et al. 2013). Influenza viruses can persist on surfaces and in the environment, allowing for indirect transmission, when pigs can become infected by coming into contact with contaminated objects, such as feed troughs, waterers, or fomites carrying the virus (Allerson et al. 2013). The high cost and difficulties in animal handling make pigs less favorable as a model for influenza virus transmission study. However, there are some studies, for example, influenza virus transmission of A/H1N1 was quantified in swine model (Romagosa et al. 2011).

7. Another animal models

and non-human primates are also can be used to study the transmissibility of the influenza virus among other models. Although cats, dogs, and nonhuman primates can be infected with the influenza virus, these animal models are not widely used.

Cats (*Felis catus*) can be infected with influenza A viruses through close contact with infected humans, other infected cats, or, in rare cases, through direct exposure to infected birds or pigs. Several studies reported cases of influenza transmission from humans to cats (Kuiken et al. 2004; Su et al. 2015). For example, during the H1N1 influenza pandemic in 2009, cases of transmission from humans to cats were documented (Löhr et al. 2010; Sponseller et al. 2010). It is important to note that while cats can be infected with influenza viruses, the transmission from cats to humans is extremely rare.

The influenza virus strains that infect dogs (*Canis familiaris)* are known as canine influenza viruses (CIV). There are two main subtypes of CIV: H3N8 and H3N2 (Crawford et al. 2005; Yang et al. 2014). CIV can spread among dogs through close contact with respiratory secretions. This typically occurs in

places with a high dog population density, such as shelters, kennels, or dog parks. Infected dogs shed the virus through coughing, sneezing, or barking, and healthy dogs can become infected by inhaling the respiratory droplets or by direct contact with contaminated surfaces. The canine influenza viruses are distinct from human influenza viruses, and human-to-human transmission of CIV has not been reported. Due to the presence of α2,3-linked sialic acid receptors in lower respiratory tract, dogs are susceptible to influenza without adaptation (Song et al. 2008). In 2015, an outbreak of H3N2 canine influenza occurred in the United States, and it was determined that the virus originated from an avian influenza strain that had adapted to infect dogs (Voorhees et al. 2017). This suggests that there can be cross-species transmission from birds to dogs, although it is not a common route of transmission.

Influenza viruses can infect nonhuman primates through respiratory droplets or direct contact. For instance, certain subtypes of avian influenza viruses (e.g., H5N1, H7N9) can infect non-human primates under experimental conditions (Kuiken et al. 2003; Fukuyama et al. 2020). Instances of transmission from non-human primates to humans are rare. Therefore, it is important to exercise caution and implement preventive measures to minimize the risk of introducing or spreading influenza viruses in non-human primate populations. Nonhuman primates can also be infected by human strains of the influenza virus and transmit the infection (Moncla et al. 2013).

Given the existing difficulties in studying influenza virus transmission in cats, dogs and non-human primates, there are no quantitative studies for these animal model.

Conclusion

This paper provides an overview of influenza virus transmission in animal models. Studying influenza virus transmission provides valuable data for ongoing research and surveillance efforts. There are numerous studies that provide insights into specific aspects of transmission, such as viral kinetics, immune responses, and the impact of environmental factors on transmission dynamics. While there may be fewer studies specifically dedicated to quantifying influenza virus transmission in animals, research involving animal models remains crucial for understanding the basic biology of the virus, evaluating vaccine candidates, and exploring potential interventions. Quantitative measurement of influenza virus transmission in animals is essential for understanding the factors influencing the spread of the virus. The combination of experimental studies and mathematical modeling provides a comprehensive approach to influenza virus studying. This knowledge is useful for such fields as the development of vaccines, antiviral treatments, and preventive measures to mitigate the impact of influenza outbreaks. This review highlights the importance of continued surveillance and control measures to prevent the emergence and spread of novel influenza strains.

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