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RESEARCH ARTICLE

Animal experiments on respiratory viruses and analogous studies of infection factors for interpersonal transmission

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Abstract

Air pollution caused by SARS-CoV-2 and other viruses in human settlements will have a great impact on human health, but also a great risk of transmission. The transmission power of the virus can be represented by quanta number in the Wells-Riley model. In order to solve the problem of different dynamic transmission scenarios, only a single influencing factor is considered when predicting the infection rate, which leads to large differences in quanta calculated in the same space. In this paper, an analog model is established to define the indoor air cleaning index RL and the space ratio parameter. Based on infection data analysis and rule summary in animal experiments, factors affecting quanta in interpersonal communication were explored. Finally, by analogy, the factors affecting person-to-person transmission mainly include viral load of infected person, distance between individuals, etc., the more severe the symptoms, the closer the number of days of illness to the peak, and the closer the distance to the quanta. In summary, there are many factors that affect the infection rate of susceptible people in the human settlement environment. This study provides reference indicators for environmental governance under the COVID-19 epidemic, provides reference opinions for healthy interpersonal communication and human behavior, and provides some reference for accurately judging the trend of epidemic spread and responding to the epidemic.

Keywords Viral transmission · Wells-Riley model · Quanta · Animal experiments · Analogous model · Finite space

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Highlights

- Errors exist in the prediction ofpropagation force due to the uncertain quanta.
- In the selection of quanta value, only thevirus species was considered.
- Complex interpersonal analogy withcontrolled animal experiment.
- Many infections of interpersonal factorscan affect the propagation force prediction.
- Expand the application of animalexperiments under epidemic prevention and control.

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Introduction

In the context of a global COVID-19 pandemic and the increasing infectivity of the mutating virus (Jin et al. 2020), the novel corona virus will most likely coexist with humans for a long time. People spend 90% of their time indoors, so control of the risk of indoor airborne infection is essential (Zhang and Lin 2021). The key point of epidemic prevention and control is to accurately describe the disease dynamics and correctly predict the magnitude of the transmission power of respiratory viruses R0 (Chen and Liao 2010). The greater the R0, the stronger the transmission power, and the stronger the ability of the virus carrier to infect the susceptible person (Pijpers 2021). Among the more common respiratory viruses, influenza viruses have an R0 of about 2 ~ 3, and SARS viruses range from 2 to 5. The transmission power of these respiratory viruses studied in this paper is similar to that of SARS-CoV-2 virus. The R0 of SARS-CoV-2 virus was about 2.2 at the beginning of the epidemic, the R0 of Delta variant was about 5.5, and the R0 of Omicron variant was about 6.0 (Bacaer and Ait Dads 2011, Chowell and Nishiura 2008, Glass et al. 2011, Johnson and Mikler

2011, Riou and Althaus 2020, Srinivasa Rao et al. 2022, Temime et al. 2021). If R0 < 1 and is persistent, it indicates that the virus is largely non-transmissible and will be gradually eradicated in this space, if R0 > 1, it indicates that the virus will be widespread in this space (Bacaer and Gomes 2009, Borowiak et al. 2020, Denphedtnong et al. 2013, Ma and Wang 2010). Therefore, the prediction of R0 has a certain reference value for judging the trend of epidemic spread more accurately and guiding human behavior better, which is very important for epidemic prevention and control. The epidemiological field usually uses the susceptible-infected-recovered (SIR), SEIR, and their extensions model to predict the statistical value of virus transmission, which is a very complex phenomenon that depends on the influence of many public policies or the intervention of technical measures (Ahn et al. 2020). The topics of existing studies and recommended technical measures were classified into three categories: public health interventions (e.g., school shutdown, home isolation, vaccine programs) (Chen and Liao 2010, Tung and Hu 2008), engineering control measures (e.g., ventilation strategies (Cooper-Arnold et al. 1999, Li 2013, Xiaolei et al. 2009), environmental decontamination measures (Brickner et al. 2003, Chen and Liao 2013, Zheng et al. 2016)), and personal protection measures (mask wearing) (Chen and Liao 2013, Fennelly and Nardell 1998, Zheng et al. 2016).

The Wells-Riley model, a cross-disciplinary approach in a multidisciplinary field, can also quantitatively analyze specific transmission cases (Aganovic et al. 2022). In the Wells-Riley basic equation, due to the data limitation caused by the complexity of reported infection cases, the quanta of known reported cases of the same virus in limited space was used to predict the infection rate in other limited space (Nardell et al. 1991). For different scenarios such as schools, airplanes, and hospitals, there is a phenomenon that quanta reference values are mixed to predict infection rates, e.g., Liao, et al. (2005) used the Wells-Riley equation to calculate the quanta of 66.91 for influenza virus in elementary schools and 28.77 for SASR virus in hospitals as references to calculate the infection rates of influenza virus in airplanes and SASR virus in elementary schools; Chen, et al. (2006) and Liao et al. (2008) used the Wells-Riley equation to calculate the quanta of 68.67 (4 ~ 12 years old) and 34.33 (25 ~ 45 years old) for influenza virus in elementary schools and 108.16 for measles virus in elementary schools as references to calculate the infection rates of influenza virus and measles virus in airplanes. The quanta calculated by this method varied widely, for example, quanta in schools is 66.91 quanta/h ~ 494 quanta/h (Chen, et al. 2006, Cheng and Liao 2013, Liao, et al. 2005); 15 quanta/h ~ 515 quanta/h in airplanes (Liao, et al. 2008, Rudnick and Milton 2003, Sze To and Chao 2010), according to which the quanta values in hospitals are 28.77 quanta/h ~ 17,730 quanta/h (Chen, et al. 2006; Liao, et al. 2005; Qian, et al. 2009), quanta in different finite spaces possess an order of magnitude difference, quanta in hospitals can even reach more than a thousand times of those in airplanes, and quanta in the same hospital environment can vary more than six hundred times.

In predicting infection rates in the literature, only considering virus species has great limitations. Many studies have shown that other technical interventions, such as respiratory protection, air filtration, and elimination, are known to have a great impact on the prediction of virus transmissible power (Liao et al. 2013); when masks are worn, fresh air changes of only 0.6 ACH can achieve the same control effect as without masks and with 2.4 ACH changes (Hu Dai 2020). Based on model predictions, for the calculated risk of TB transmission in hospitals, wearing a surgical mask ($\eta = 0.58$) reduces the probability of infection per susceptible individual from approximately 15% to about 7%, a respirator with high efficiency filtration ($\eta = 0.98$) reduces the risk of infection to about 0.3%, and PAPRs with a flexible semi-mask ($\eta = 0.996$) reduce the risk of infection to 0.02% or so (Nazaroff et al. 1998); according to Chen and Liao (2008), for the risk of transmission of influenza in schools, the risk of transmission corresponds to 15%, 12%, 8%, and 2% when the efficiency of respiratory protection is 0.6, 0.7, 0.8, and 0.95, respectively, showing a significant reduction in the risk of transmission; Miller-Leiden, S. Lobascio et al. predicted that the results obtained the filtered air circulation rate increases from the baseline condition of 2 h^{-1}. The average steady-state indoor particle concentration can be reduced to 33 ~ 56% of the baseline value when the filter air circulation rate is increased from the baseline condition of 2 to 6 h^{-1} and to 3 ~ 21% of the baseline value when it is increased to 12 h^{-1}. In realistic infection scenarios, various factors in the human habitat, such as the number of infected cases, the duration of exposure of susceptible groups, and the mode of contact between individuals, are difficult to define precisely. For example, for household aggregated outbreak transmission, close contact is far more likely to occur in shared living spaces and can trigger COVID-19 infection rates of almost 30% or more (Jing et al. 2021). In March 2020, a superspreading event broke out in Washington (Hamner et al. 2020); in March 2020, 2.5 h of singing practice and close contact behaviors such as members sitting close to each other, sharing snacks, and stacking chairs at the end of practice provided multiple opportunities for droplet and contaminant transmission, and the potential for members to meet privately, resulting in a maximum infection rate of 86.7%; in an outbreak of infections in a restaurant in Guangzhou, China (To et al. 2020), the complexity and uncertainty of human movement trajectories led to the difficulty of studying the degree of influence of various factors on quanta. Quanta serves as a way to calculate unknown spatial infections based on known cases of infection and thus to obtain the transmission power of that space. In addition to the parameters calculated in the Wells-Riley equation, existing studies have found that the magnitude of viral transmission is influenced by the environment and the state of the human host (Basu and Galvani 2008). When the virus spreads in different regions or countries, the impact of the local environment, economy, population, and social policies needs to be taken into account. Avelino Nunez-Delgado reports on Italy in relation to the second wave of COVID-19 infections in Europe (Nunez-Delgado et al. 2021), showing that areas with often high levels of air pollution have seen higher numbers of COVID-19-related infections and deaths (Coccia 2020a, Sarkodie and Owusu 2020), as well as evidence of the impact of wind speed on transmission (Coccia 2020b). COVID-19 is sensitive to temperature. Temperature and humidity are the most important factors affecting the spread of SARS-CoV-2, while other meteorological factors also have an impact, but they are not the main contradiction affecting its spread and are affected by other social factors and human factors (Srivastava 2021). Bontempi and Coccia (2021) use international trade as a key parameter for the spread of COVID-19, and analyses looking back at the spread of past epidemics show that the virus spreads faster during periods of economic prosperity, which can be attributed to increased travel by people, followed by increased human interaction. At the same time, high-income countries and countries with more active import and export trade have been shown to have more complex economic and social interactions, resulting in higher rates of disease transmission than countries with low and middle income or high unemployment (Bontempi et al. 2021, Coccia 2021). At the same time, the possibility of cluster infection will increase correspondingly in areas with high population density (Bontempi et al. 2021). In addition, it is still affected by many factors, and the complexity of human-to-human transmission makes it difficult to study the influence of other factors (Li et al. 2021).

In contrast, in medicine, infection experiments between animals are usually used to study the magnitude of virus transmission. Rodents are ideal models for studying the spread of viruses because they live in dense, highly social groups and harbor many pathogens. Rodents are also diverse, and the effect of distance on transmission can be assessed. In addition, rodents are common laboratory animals, and there are readily available tools to study their immune responses (Fay et al. 2021). Liu Kaituo analyzed the pathogenicity and transmissibility of avian influenza virus in mammals with the help of mouse experiments, obtained the virulence of different viruses in mice, and judged the affinity for human receptors (Liu et al. 2022). Jessica A. Belser uses ferrets as an alternative model to study the transmission mechanism of influenza viruses, but cross-laboratory comparative analysis of experimental data can be difficult to interpret due to differences in virus transmission procedures, cage design, airflow direction, air exchange frequency, or environmental conditions (Belser et al. 2022). Huang, Y. Selected ferrets from transgenic mice, Syrian hamsters, ferrets, and non-human primate models based on the experience of previous literature as alternative models to study influenza virus transmission (Huang et al. 2022).

In contrast to epidemiological calculation methods that use human reported cases to predict transmission, the environment of animal experiments conducted in medicine can be predetermined; the physical space where infection occurs, the geometry of the environmental chamber, temperature, and relative humidity can be artificially regulated; and experimental conditions can all be guaranteed to fluctuate within a reasonable range, with the source of infection. The airflow between them is directed from infected animals to susceptible individuals using natural ventilation or through mechanical air blowing, e.g., Hao et al. (2019) in the guinea pig experiments conducted in the environmental simulation chamber with a preset ventilation rate value of 144.4 m^3/h; Zhang et al. (2013) in the ferret experiments conducted in the environmental simulation chamber was 148.5 m^3/h, which allowed precise control of the ventilation rate, an important parameter in the prediction of propagation using the Wells-Riley equation, and ensured the accuracy of the external conditions in the first place; the number of infected animals was as low as one or two (Yen et al. 2005) and as high as eight or nine (Eaton 1940). The number of susceptible animals is also set at a ratio of 1:1 to 1:2 depending on the number of inoculated animals (Kim et al. 2020, Pacheco et al. 2012). The number of infected animals and susceptible animals can be determined. The amount of virus infection in animals was set according to the type and weight of experimental animals. The viral load and pathogen concentration were determined by quantitative inoculation, titration of contaminated surfaces, and release of toxic fog etc. (Mubareka et al. 2009, van Doremalen et al. 2020); Eaton (1940), (Steel et al. 2009), Lv et al. (2012), Rimmelzwaan et al. (2006), Martina et al. (2003), Zhou et al. (2021), Richard et al. (2020), Chan et al. (2020), Schlottau et al. (2020), Kim et al. (2020), Sia et al. (2020), and Jerome L et al. (Schulman and Kilbourne 1963) placed experimental animals in the same steel cage so that the animals could be in sufficiently close contact with each other. Lowen et al. (2006), Juleff et al. (2013), Zhang et al. (2013), Asadi et al. (2020), and Gustin et al. (2015) used a wire mesh to divide adjacent experimental animals to reduce the contact area and contact probability between experimental animals. Hao et al. (2019) and Lv et al. (2012) place the experimental animals in the environment of the two different cases; adopt the way of ventilation pipe connection blocks the direct contact between animals; and ensure that only the single way to aerosol transmission, through the experiment device of limit and the requirement of experiment conditions between the infected animals and exposed susceptible animals contact way and locus of control, maintains the frequency of daily or bi-dayly testing of susceptible animals to ensure that the length of exposure can be determined when infection rates reach a stable level. Therefore, the animal infection experiment creates good conditions for studying the infection in the process of human interaction and provides accurate data support for scientific prediction.

Through multiple interpersonal interaction infection process literature-based evidence, a categorical comparison of quanta calculated from interpersonal infection processes in the same finite space, considering only the influence of the factor of virus species, when applying quanta for virus transmissibility prediction, revealed excessive differences that affected the accuracy of using quanta to predict virus transmissibility in different spaces. By dissecting the controllability of external factors and internal condition parameters in animal experiments, and the similarity between animal exposure and interpersonal interaction during infection with respiratory viruses, an environmental simulation chamber experiment of inoculation-producing infected individuals was chosen to analogize the process of respiratory virus infection in the human habitat, and an analogical model was developed to explore some common patterns in the process of calculating quanta values, based on the Wells-Riley equation between the two, and to find infection factors that may affect quanta values, and to provide a reference for improving the accuracy of quanta values taking in infection rate prediction.

Basis of analogy between experiments on animal transmission and human transmission

Physiological parameters and environmental conditions

In medical studies, SARS-CoV-2 when interpersonal transmission is high, it is not possible to conduct direct experiments on virus transmission in humans due to the extremely pathogenic nature of the virus itself and the ethical limitations of human experimentation, so analogous experimental studies are often conducted with the help of experimental animals as a reference (Wenbo 2010). For physiological parameters such as body temperature, chromosome count, total leukocyte count, and whole blood volume, the differences between experimental animals and humans are not significant; as shown in Table 1, although the body temperatures of experimental animals are all slightly higher than those of humans, both

Table 1 Physiological parameters of experimental animals and humans (Enqi et al. 2008)

Physiological parameters	Experimental animal species				Humans
	Mice	Rat	Guinea pig	Ferret	
Adult weight (g)	18 ~ 40	180 ~ 350	400 ~ 750	250 ~ 350	45,000 ~ 70,000
Body temperature (°C)	37 ~ 39	37.8 ~ 38.7	38.9 ~ 39.7	37.8 ~ 40	36 ~ 37
Number of chromosomes (2n)	40	42	64	40	23
Total white blood cell count (10^3/mm^3)	5.1 ~ 11.6	8.7 ~ 18	8.7 ~ 18	4.3 ~ 7.1	3.5–9.5
Whole blood volume (mL/100 g)	5.85	2.75 ~ 6.99	5.75 ~ 6.99	5 ~ 7	6.5–9.0
Respiratory rate (times/min)	84 ~ 230	66 ~ 114	69 ~ 104	33 ~ 36	12 ~ 20
Tide volume (mL/time)	0.54 ~ 0.64	1.1 ~ 1.6	1.2 ~ 1.9	4.2 ~ 6.7	400 ~ 500
Pulmonary ventilation rate (mL/min)	45.36 ~ 147.2	72.6 ~ 182.4	82.8 ~ 197.6	138.6 ~ 241.2	4800 ~ 10,000

animals and humans are thermostatic, and the transmission characteristics of the virus between animals and its replication in animals are similar to human infection, with the same ACE2 capable of binding to SARS-CoV-2 receptors (Hoffmann et al. 2020) and similar disease symptoms such as cough and shortness of breath, although the chromosome count and total leukocyte count are slightly higher in experimental animals. Humans and animals have complex genetic states and high immune response levels, which are conducive to reproducing the clinical features, viral dynamics, histopathological changes and immune responses of animals during viral infection, thus reproducing the pathogenic characteristics of RNA pathogens and the defense process of the human immune system against pathogen invasion (Enqi et al. 2008). The clinical features, viral kinetics, histopathological changes and immune responses in animals are similar to those in humans (Chan et al. 2020, Kim et al. 2020, Mubareka et al. 2009, Schlottau et al. 2020). On the other hand, due to the physical differences between animals and humans, the smaller the body weight of an organism, the higher its respiratory frequency and the smaller its tidal volume, but because the difference in tidal volume between animals and humans is too large, the lung ventilation rate in humans is much higher than that in animals, so the total amount of pathogen production and excretion per unit time and the proportion of space occupied by body weight need to be considered next.

Animal experiments are generally conducted in laboratories with high-level biosafety protection for dissemination studies. The basic survival and activities of experimental animals are met under the premise of considering safety issues and simulating human living space environmental conditions in terms of temperature and humidity as much as possible, as shown in Table 2. In terms of ambient temperature, relative humidity, wind speed, etc., the animal experimental space environment has some similarity to the environmental conditions of the human living space.

Modes of exposure to infectious agents

Different forms of contact and communication between individuals can lead to differences in the way they are exposed to infectious agents, and as herd animals like humans, laboratory animals are very similar to humans in terms of activity patterns. Although the dimensions of the various types of environmental chambers used for animal experiments vary, the trajectories of the animals are restricted to some extent depending on the content of the experimental study to simulate the range and form of human activity.

Table 2 Comparison of environmental parameters of human settlements and animal experiments (Eaton 1940, Lv et al. 2012, Schulman and Kilbourne 1963, Zhang et al. 2013)

The environment in which	Physical parameters	Temperature (°C)	Relative humidity (%)	Wind speed (m/s)
Habitat	Reside	18～28	30～70	≤0.5
	Office	18～28	30～70	≤0.5
	Trade	16～30	30～70	≤0.5
	Public	18～28	40～80	≤0.5
Animal experiment box	Guinea pig	20～22	30～40	0.33
	Ferret	20～22	30～40	≤0.5
	Swiss rat	Indoor temperature	30～70	≤0.5

Respiratory infection viruses are known to be transmitted between susceptible populations in four broad ways (Organization 2021): (1) direct physical contact with an infected person; (2) proximal droplet transmission, i.e., inhalation of infectious secretions such as respiratory secretions or droplets released by an infected person; (3) transmission by contact with surfaces contaminated with the virus; (4) airborne transmission, caused by the long-distance, prolonged suspension in the air and still infectious aerosol. Infection due to diffusion (Xiao et al. 2018), which can correspond to the forms of infection prevalent in existing experimental animal models, in order of proximity contact experiments, vector-borne experiments, and aerosol transmission experiments, is shown in Fig. 1, using animal infection experiments in a controlled and limited space to simulate infection scenarios during human interactions, where infected animals obtained by artificial inoculation represent infected individuals in an infectious disease outbreak scenario, and where they are placed with similar healthy animal individuals, i.e., representing interpersonal. The animals are placed in the same confined space with similar healthy animals, representing susceptible individuals in human interactions.

Proximity contact transmission experiments between animals usually place inoculated animals and exposed animals in the same rearing cage or neighboring cages at very close distances, where the inoculated animals and exposed animals do not act aggressively toward each other and where there is some degree of physical contact, as shown in Fig. 1 (A) for the same cage experiment and Fig. 1 (B) for the neighboring cage experiment, which can simulate virus transmission through direct human interactions experienced by infected and exposed individuals in the course of the pathway of virus transmission through large direct physical contact such as hand shaking, hugging, and kissing and closer meetings, dinners, or offline trade practices such as imports and exports, when there may be a small probability of touching events; vector transmission in experimental animals usually places the vector dripping with virus inside the experimental animal's feeding cage; and the location where the

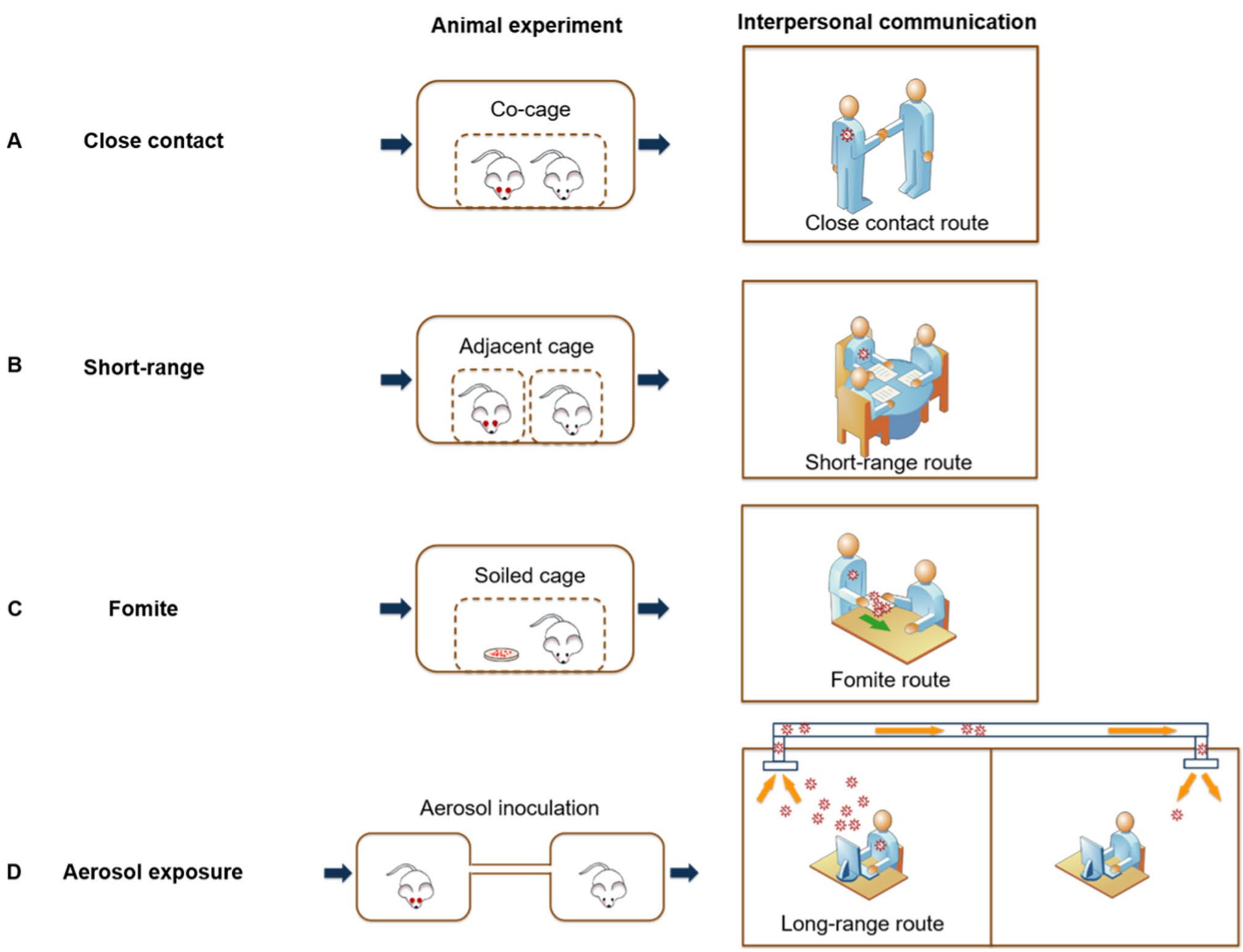

Fig. 1 Similar correspondence between animal experiments and human transmission modes under four types of transmission routes

experimental animal is guaranteed to have access to this vector. As shown in Fig. 1 (C), it is possible to simulate transmission through a vector object when a susceptible person touches an object or location that the infected person has touched within a short period of time, such as receiving and distributing assignments in a classroom, passing information in an office, or online shopping through e-commerce; aerosol transmission in laboratory animals usually refers to transmission that occurs when the infected person and the exposed person do not come into direct physical contact but are separated by a distance but are still in an integrated environment. Virus transmission, as shown in Fig. 1 (D), is simulated by placing cages ducted together or at intervals to simulate the risk of long-distance transmission in human interactions, while additional directional airflow is needed to simulate the movement of airflow organization due to ventilation or air conditioning systems in human living environments and to explore the risk of virus transmission in the corresponding situations, which can be simulated when people are in environments such as cinemas, airports, and hotels. It is possible to simulate infection when people are seated at a distance or when rooms are connected by air conditioning systems in environments such as cinemas, airports, and hotels.

In summary, based on the similarities in various aspects such as physiological parameters, environmental conditions, and modes of exposure to the source of infection, it can be judged that animal experiments are similar to interpersonal processes in many key aspects (Feng et al. 2016), and it is reasonable to make analogies (Xiongfei 2014), so that some phenomena from animal infection experiments can be used to explain difficult questions about interpersonal transmission processes (Bing 2016, Yuan et al. 2021) and to lay the foundation for analogous modeling.

Analogous models

Sample and data

The focus of this study is the infection of animals in the environmental chamber and the process of virus infection in indoor interpersonal communication under different circumstances. When analogies are made between controlled animal experiments and complex interpersonal processes and animal models are established, physiological parameters such as lung ventilation and indoor ventilation and environmental parameters such as animals and humans need to be used. Therefore, the content of this study is highly relevant to biological health and habitat environment.

Measures of parameters

- Indoor airflow cleanliness index R_L

Given the large differences in the values of the model variables I, p, t, and Q when using the Wells-Riley equation to calculate the animal infection experiment and the human interaction process, it was not possible to control for a single variable when wanting to compare the quanta of the two, so an analogy was considered by constructing a dimensionless indicator.

Dimensionless parameter provides insight into the nature of the commonality of things, i.e., the intrinsic connection of things. Dimensionless quantities can be used to represent the laws of things, as analogous indicators for comparison and generalization to groups of similar phenomena or to discover similarities between phenomena. Therefore, in order to obtain the link between animal experiments and the process of human interaction infection, firstly, the appropriate variable parameters in Wells-Riley model are taken and dimensionless, and in the process of back-calculating quanta values using the Wells-Riley model, the four variables of number of infected persons I, lung ventilation p, exposure interval t, and room ventilation Q are involved. Based on the quanta analysis, the three major model variables I, p, and Q were selected to construct the analogous reference indicator R_L, and R_L was expressed as:

$$R_L = \frac{Ip}{Q} \tag{1}$$

From the expression, it can be seen that the dimensionless parameter R_L was constructed by choosing the three variables of the Wells-Riley model, the number of I-infected persons, the p-lung ventilation rate (m^3/h), and the Q-room ventilation rate (m^3/h); the magnitude of the lung ventilation rate represents the rate of exhaled gas and characterizes the amount of pathogens exhaled per minute by SARS-CoV-2 patients, thus R_L characterizes the patient's exhaled ratio of the total volume of contaminated gas to the efficiency of clean outdoor gas exchange, i.e., the ratio of pathogen output to emission in a confined space, and its physical significance is expressed as the degree of contamination of the air in the room under the influence of airflow organization, which is an important factor influencing the number of pathogens inhaled by susceptible individuals and is therefore defined as an indicator of indoor airflow cleanliness as an analogy between animal infection experiments and human-to-human transmission.

This indicator takes into account both the variation in the number of infected individuals and the difference in lung ventilation rates between animals and humans.

In animal experiments, often the number of inoculated animals is slightly greater than the number of infected individuals during human interaction infections, and in most cases of human-inhabited infections, there is transmission from one infected individual to multiple susceptible individuals, whereas inoculated mice in animal transmission experiments are generally 3 to 8 (Chan et al. 2020, Colenutt et al. 2016). The human lung ventilation rate is tens to nearly a hundred times higher than that of animals, and the data in Table 2 can be converted to show that the lung ventilation rate of animals fluctuates in the range of 0.0027 ~ 0.0145 m^3/h, and the human lung ventilation rate varies in the range of 0.288 ~ 0.6 m^3/h, and the magnitude of the lung ventilation rate determines the number of exhaled pathogens to a certain extent, so that in a certain time in a limited space, the total number of pathogens exhaled by a human infected person is tens of times greater than that exhaled by a total inoculated animal. From the point of view of dilution or expulsion of pathogens, in animal experiments, the number of air changes in the experimental space often greater than 8 times/h. The volume of the experimental chamber usually varies in the range of 0.006 ~ 3m^3, so that the total number of experimental animals varies in the range of 10 ~ 20, and the magnitude of ventilation required is about 0.5 (m^3/(h-animal)), while in the architectural human environment, with reference to most experimenters in the value of the ventilation rate set in the experiment and the provisions in ASHRAE Standard 170–2021 “Ventilation in Health Care Facilities” (American Society of Heating, Refrigerating and Air-Conditioning Engineers 2021), “Design Code for Heating Ventilation and Air Conditioning” (GB 50,736–2012) (China 2012), and Public Transportation Health Standards (GB9673-1996) (National Health and Wellness Commission of the People's Republic of China 1996) in residential, office buildings, and public transportation places per capita, the minimum fresh air volume per capita is 30 (m^3/(h-people)) and 20 (m^3/(h-people)) in commercial buildings. Thus, the size of the ventilation rate in a human environment is similarly tens of times greater than in animal experiments.

Therefore, as long as it is ensured that the ratio of exhaled gas to ventilation rate, i.e., the pathogen production and emission ratio, in the human habitat environment tends to increase in equal proportion compared to animal experiments, i.e., the R_L for animal experiments and the R_L for the human interaction infection process are similar, then it can be assumed that the animal experiments and the human interaction infection process have similar exhaled gas rates, and room air exchange is comparable.

- Space occupancy ratio

Because the volume of the animal is much smaller than the volume of the human body, and the volume of the environmental box in which the animal is located is also much smaller than the volume of the human living space, it is difficult to maintain consistency in individual factors, but analogies can be made by means of calculating the ratio of the animal or human in the space in which they are located, i.e., in a way that the ratio of the animal volume to the environmental box volume is similar to the human volume to the volume of the human living space. As shown in Fig. 2, similarity of spatial occupancy is achieved when the weight of the human is 200 times the weight of the animal, and the volume of the space the human is in is likewise 200 times the volume of the environmental box in which the animal is experimenting, defining the ratio of weight to environmental volume as the spatial occupancy ratio.

Models and data analysis procedure

- Basic model

The important parameter of quantum productivity, defined as the airborne nuclear dose of droplets required to cause infection in 63% of the susceptible population (Wagner et al. 2009), is a useful indicator of the amount and pathogenicity of infectious material present in the air, as well as the average susceptibility of the susceptible population (Mushayabasa 2013). The Wells-Riley equation (Riley et al. 1978), on the other hand, was proposed in 1978 by Riley and his colleagues in an epidemiological study of measles outbreaks based on Wells and relates the infection rate of the virus to the quanta value by the equation expressed as:

$$P_I = \frac{C}{S} = 1 - \exp\left(-\frac{Iqpt}{Q}\right) \quad (2)$$

where P_I is the probability of infection (%), C is the number of outbreak infection cases, S is the number of susceptible people, I is the number of infected people, p is the lung ventilation of a person (m^3/h), q is the quanta productivity (quanta/h), t is the exposure time interval (h), and Q is the amount of room ventilation (m^3/h).

The Wells-Riley equation has become a universal method for calculating the process of human interaction infection, and literature exists on the use of the Wells-Riley equation to calculate quanta values in animals in different settings (Haoran 2021), and it was found that the Wells-Riley equation is also applicable to experimental animal models of infectious diseases, and in order to explore the factors that affect the quanta during the prediction of viral transmissibility quanta, this paper applies the classical quantitative assessment of respiratory diseases risk of infection through airborne transmission. The Wells-Riley model was used in the animal experiments to infer infection factors affecting transmission prediction during human interaction by establishing analogous reference indicators.

- Data analysis procedure for animal experiments

During the calculation of quanta values for human cases of limited space infection, most viral quanta values are obtained by back-calculating the parameters of known cases through the Wells-Riley equation (Nardell et al. 1991), and using this as a basis, the quanta back-calculation equation for animal experiments using the indoor airflow cleanliness index R_L defined in this study is as follows:

$$q = -\frac{1}{R_L t}\ln\left(1 - P_I\right) \tag{3}$$

In the process of calculating the quanta for animal experiments, the infection rate and exposure time are taken into account, and the change law of the infection rate of experimental animals in different days of exposure is characterized by Fig. 3. According to this law, we imitate the way of extracting the infection rate in known human cases and disregard the stage of decreasing the infection rate caused by the animals' own resistance to the virus and take the value of the infection rate and exposure time in animal experiments when the infection rate reaches the maximum value, so as to ensure the consistency of the determination law of the infection rate in animal experiments and known human cases.

Infection factors

Viral load of infected persons

- Symptoms of infected persons

Referring to the NIH COVID-19 treatment guidelines, we classified patients infected with SARS-CoV-2 according to disease severity as asymptomatic or presymptomatic infection, mild illness, moderate illness, severe illness, and critical illness (COVID-19 Treatment Guidelines Panel 2022). Patients with different symptoms and different behavioral states will then correspond to different respiratory rates and release different levels of viral particles. For example, in the experiments of Heon and Suckho (2021) and Buonanno et al. (2020), the amount of virus in the exhaled breath was measured to give quanta of 5 quanta/h for asymptomatic infected patients under relatively static conditions, 76 quanta/h under light work talk conditions, and 490 quanta/h under noisy talk conditions, almost a hundred times higher than under static conditions, while the back-calculated quanta values for symptomatic infected patients under general conditions had only the quanta for symptomatic infected persons under general conditions of also only 100 quanta/h.

With the help of Gustin et al. (2011)'s experiments in which tests of exhaled air from ferrets were analyzed, there was a significant difference in the particle size distribution between normal breathing and sneezing, as shown in Fig. 4, with coughing and breathing producing particle sizes in the 0.5–15-μm range, whether

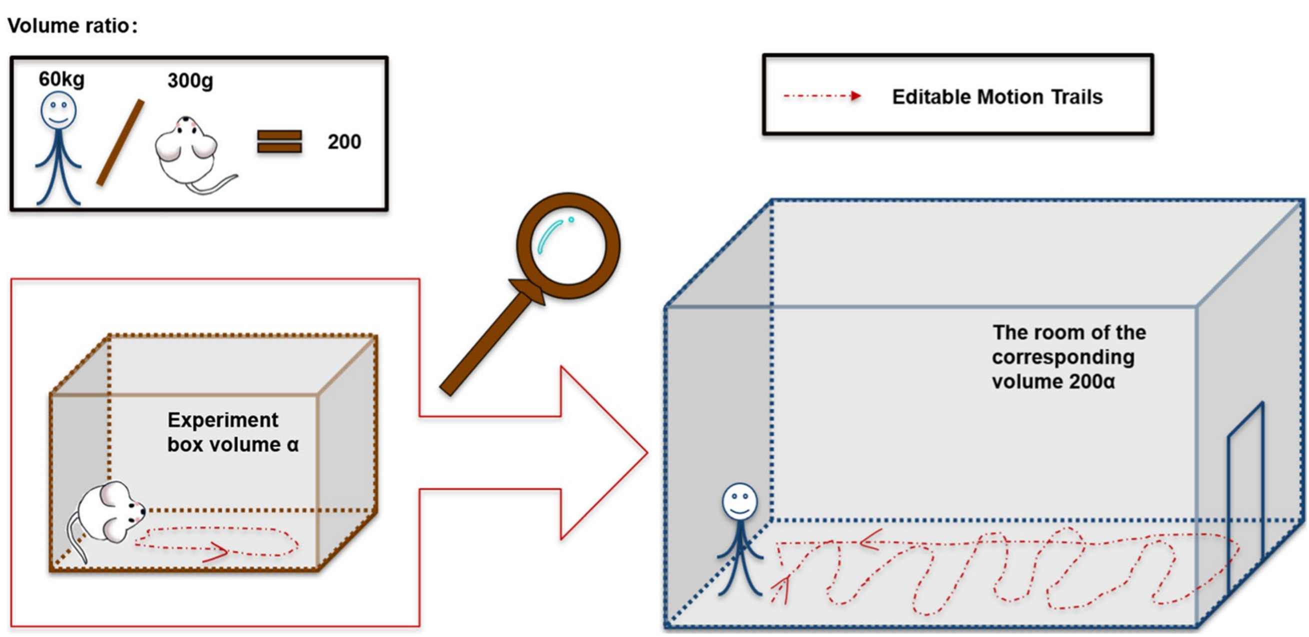

Fig. 2 Percentage of space for experimental animals vs. space for human habitat

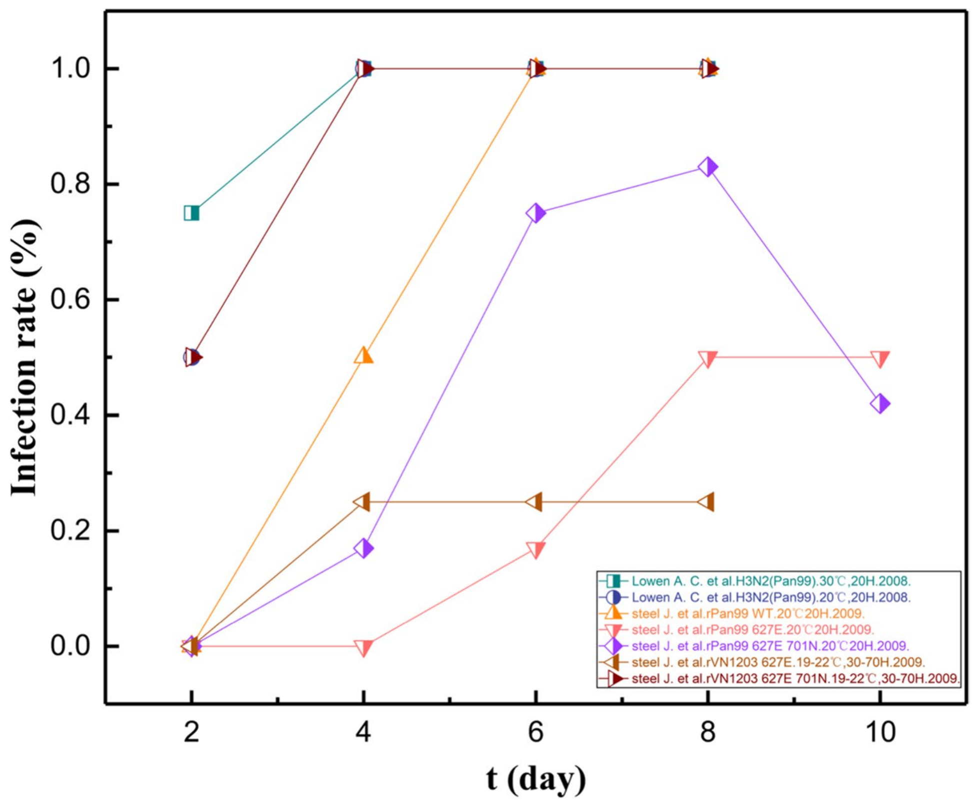

Fig. 3 Trend of infection rate in animal experiments with exposure time

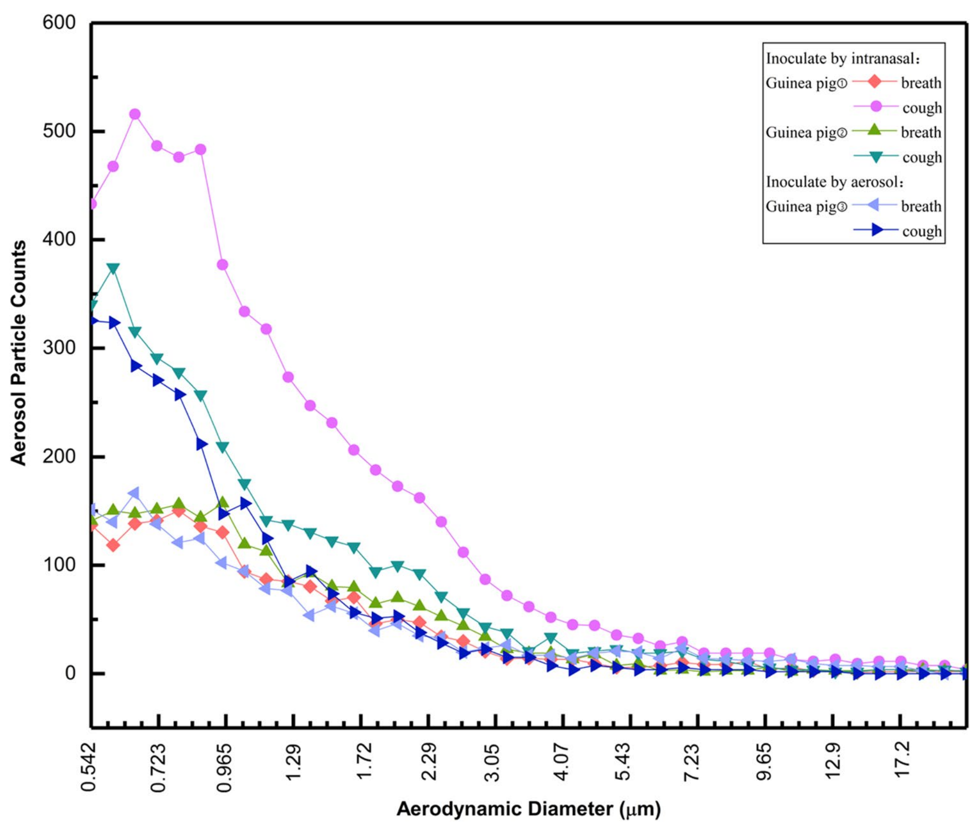

Fig. 4 Trend of the number of exhaled particles in ferrets as a function of particle size

inoculated by intranasal or by aerosol infection with H_3N_2 influenza virus (A/Panama/2007/1999; PN99) ferrets, the number of aerosol particles released decreases with increasing particle size, and the number of aerosols is already close to 0 when the particle size is greater than 5 m. And it is clear from the figure that the total number of particles released during coughing is much greater than that during breathing, and that more than three times as many aerosols less than 1 m are released during coughing as during breathing; for the same particle size, the difference between the number of particles released from coughing and breathing can be up to four times larger, while the size of particles released by a person during coughing is also tens to hundreds of times larger than during breathing (Jung et al. 2022). It has been reported that patients with COVID-19 suffer from symptoms such as dry and short coughs and that different cough mechanisms may produce carrier droplets of different sizes (Ghinai et al. 2020). With the help of the pattern of animal experiments, we can see that determining the presence or absence of symptoms and the state of the infected person affects the size and number of particles exhaled by the patient, with the more severe symptoms releasing a greater number of droplet particles as a direct cause of the larger quanta.

- Number of days the infected person has been ill

The rate of virus release varies with the number of days the infected person has been ill. In Qian et al. (2009)'s study, the quanta values satisfy the law of the Wells-Riley model and increase with the increase of ventilation rate Q. It is also influenced by the number of days the infected person is sick, i.e., the viral load of the patient. Figure 5 shows the variation of quanta with the number of days the patient is sick, and it can be seen that at different ventilation rates, the quanta on the third day after the patient was admitted to the ward since March 4 were on average higher than quanta by the fourth day of the experiment, which, by analyzing the experiment, could be due to the peak viral load in the infected patients on the third day of the experiment.

With the help of Lowen et al. (2008) and Steel et al. (2009)'s guinea pig experiments, the viral load of inoculated guinea pigs generally decreased with increasing time of inoculation, but there were still some guinea pigs in which the viral load did not reach its peak until 3 ~ 5 days after inoculation, and the viral load of susceptible guinea pigs

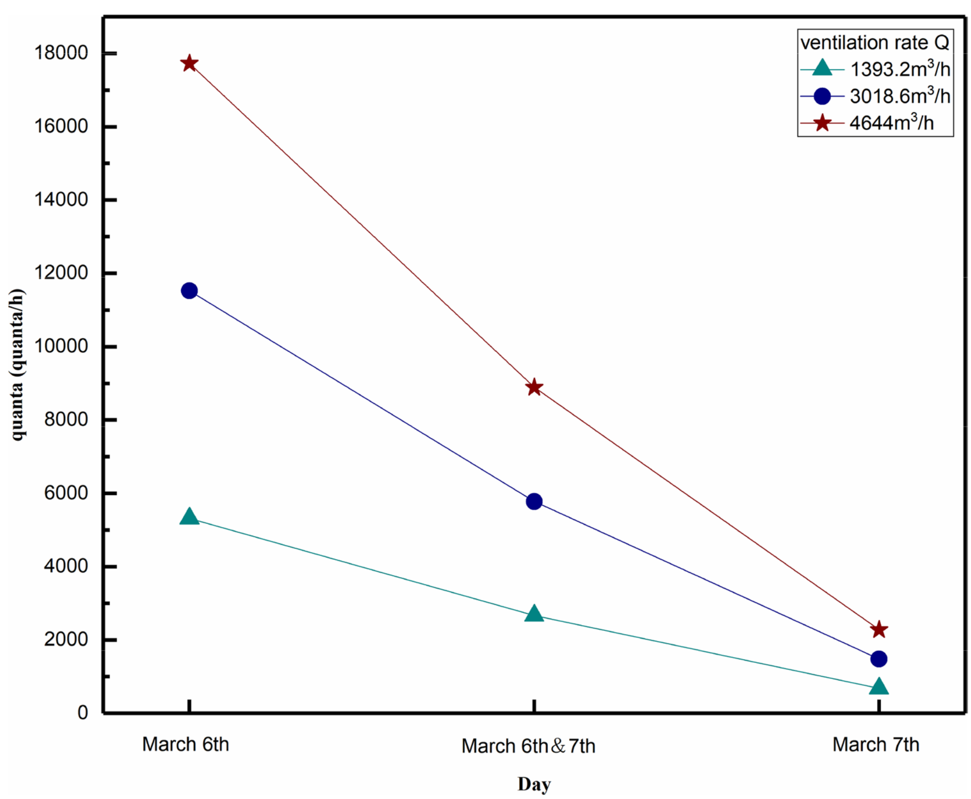

Fig. 5 Trend of quanta with the number of days of illness at different ventilation rates

generally increased with increasing time of inoculation, as shown in Appendix A: Figure A.1 and Figure A.2. Therefore, when making predictions of infection rates, choosing similar levels of illness and the same number of days of illness would make the selection of quanta more accurate.

Inter-individual distances

Unlike places where intimate contact is often present, such as the home, people are often required to maintain a certain vaccination distance from each other when in public due to public health interventions, and the survivability of the virus during transmission is particularly important when there is a difference in distance between the infected and susceptible person. Whereas differences in environmental factors such as temperature, humidity, and ultraviolet radiation (UV) can affect the survivability of airborne organisms, for cities with four distinct seasons, temperature and humidity vary over time throughout the year, and even in cities in tropical climates, temperatures vary in the 20 ~ 30 °C range throughout the year; for example, in the guinea pig model experiments of Lowen et al. (2008), 30 °C ambient temperature blocked aerosol transmission of influenza virus between guinea pigs by acting on the host to release the virus, but in the proximity model experiments, 30 °C still had high infection rates of 75–100% when the humidity changed from 20 to 80%, while the proximity model experiments at 20 °C humidity had higher infection rates than at the same temperature and humidity using aerosol transmission model of John Steel's guinea pig experiments.

Although droplet sizes expelled by all types of respiratory activity range widely, droplets larger than 100 μm usually cannot travel long distances or will evaporate rapidly during transport (Jung et al. 2022), so most droplet sizes in aerosol propagation experiments are much smaller than in close contact experiments. At the same time, longer-range transport requires consideration of the effects of airflow organization on aerosol particles and inevitably suffers from uncertainty in the respiratory deposition of airborne pathogens due to air turbulence, which directly affects the intake of airborne pathogens (Sze To and Chao 2010). Even for similar finite spaces, differences in exposure patterns leading to different propagation distances have a large impact on the quanta values taken.

The relationships between experimental animals can be classified according to the distance into three categories, such as co-cage, cage-to-cage, and other close contact relationships with a greater probability of exposure, and long-range aerosol diffusion relationships where only aerosol diffusion propagation is present. From Fig. 6, it can be seen that the quanta calculated when animals are caged together for experiments are significantly larger than those calculated for cage-to-cage and long-distance aerosol experiments, while the size of the circle qualitatively indicates the closest contactable distance between susceptible and infected; the larger the circle, the closer the distance between animal cages will be, and the

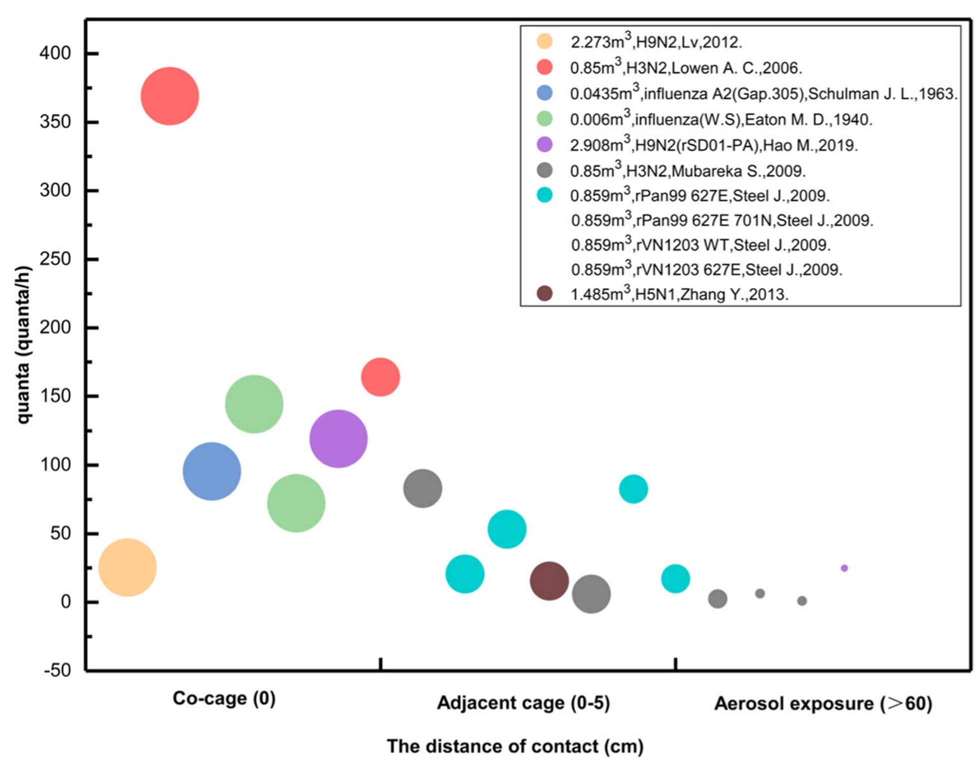

Fig. 6 Variation pattern of quanta with animal contact distance

shortest distance is 0, i.e., the animals are caged together, and it can be seen that in experimental animals in the same kind of distance relationship, subtle distance differences have little effect on the quanta; therefore, the difference in distance between individuals due to different contact methods is another major factor affecting the variation in the calculated quanta, and thus, the nature of the space in which the original case is located and the closest distance that the person may be in contact with should be noted when the quanta is selected, providing another reference factor for the selection of the quanta.

Discussion

Example of quanta calculation for animal analogy experiments

Two animal experiments were selected for analogy with the human interaction infection process, respectively, to compare the calculated quanta values of the animal experiments with the quanta values calculated from the human interaction process, which have similar analogous reference indicators to the human interaction infection cases.

The values of the analogous reference index R_L and the space-occupancy ratio are analyzed and listed in Table 3, and the values of the index R_L were similar in both analogous experiments, calculated for each analogous test of the interpersonal interaction infection process and the animal analogous experiment, respectively. In the analogous 1 experiment, according to Hao et al. (2019) in 2019, the R_L index of the animal experiment was calculated to be about 1.2×10^{-4} and Qian et al. (2009) and Cheng and Liao (2013) calculated the R_L index of the human interaction infection process to be about 1.2×10^{-4} and 1.6×10^{-4}; in the analogous 2 experiments, Zhang et al. (2013) and Sze To and Chao (2010) calculated that the R_L index for both the animal experiment and the human interaction infection process was 1.8×10^{-4}, so it can be assumed that the total concentration of exhaled pathogens in the two types of experiments conducted separately for the analogy is similar to the indoor air exchange; the most common per capita weight of 60 kg was taken for the calculation of the space share, and in the analogy 1 experiment, Hao et al. (2019) placed 250 g of guinea pigs in an environmental chamber close to 3 m^3 and were calculated to obtain a space occupancy ratio of 8.6%, which is similar to Qian et al. (2009) and Cheng and Liao (2013) who calculated 8.2% and 9.5% space occupancy in hospitals and schools, respectively. In the analogous 2 experiment, Zhang et al. (2013) and Sze To and Chao (2010) calculated spatial occupancy ratios of 33.7% and 35.7% for animal experiments and human interaction infection processes, respectively, so it can be confirmed that the analog 1 and analog 2 experiments have similar spatial occupancy ratios, respectively, and thus, the quanta values calculated for the two analog experiments are compared separately.

Comparing the selected animal experiments with the analogous index of the human interaction infection process R_L, the difference between the values taken always remained within 0.4×10^4; the difference in the ratio of space accounted for no more than 10% when in similar conditions; the two cases of animal experiments were selected on the basis of similarity with the human interaction infection process, and the two analogous experiments also basically represent the most common transmission routes in human interaction. In the guinea pig experiment conducted by Hao et al., the positional relationship between guinea pigs was isolated by environmental boxes, one part of which could be directly contacted, while the other part could only be transmitted by long-distance aerosol transmission of duct transport airflow, similar to the state humans are in in classrooms and multi-bed isolation wards; in Zhang et al.'s experiment using female ferrets and guinea pigs, the animals were in close proximity to each other but not in direct contact through the confines of a steel cage and could be transmitted by droplets between them, similar to the process of human interaction in an airplane.

However, the quanta values calculated from the human interaction infection process and the animal analog experiments, which are supposed to be similar, still have some differences. As can be seen from Table 4, during

Table 3 Calculated values of R_L and spatial proportions for the human interaction infection process and animal analogy experiments

	Literature sources	R_L ($\times 10^{-4}$)	Weight (kg)	Volume of space (m^3)	Space ratio (%)
Analogy 1	Yi-Hsien Cheng	1.58796	60	629	9.5
	Hua Qian	1.19261	60	729	8.2
	Mengchan Hao	1.24644	0.25	2.908	8.6
Analogy 2	Sze To G. N	1.83381	60	168	35.7
	Ying Zhang	1.81818	0.5	1.485	33.7

Cheng and Liao (2013), Hao et al. (2019), Qian et al. (2009), Sze To and Chao (2010), Zhang et al. (2013)

Table 4 Interpersonal infection process and animal analogy experiment quanta calculated values

Access way	Literature sources	Object	Exposure time (h)	Quanta release rate (quanta/h)	Quanta release (quanta)	Infected/Susceptible (I/n)	Type of virus	Space
Analogy 1	Yi-Hsien Cheng	Human	6.36	222	1411.92	1: 42	HINI	Classrooms
				162	1030.32		H3N2	
				161	1023.96		Type B	
				494	3141.84		P-H1N1	
	Hua Qian	Human	0.67	11,526	7722.42	1: 10	SASR	Isolation ward
				1482	992.94	1: 9		
				5778	3871.26	1: 19		
	Mengchan Hao	Guinea pigs (250 g)	24	119.23	2861.52	1: 2	H9N2(rSD01-PA)	Co-cage + Pipeline propagation
Analogy 2	Sze To G. N	Human	3.33	515	1714.95	1: 74	Influenza	Aircraft
	Ying Zhang	4-month-old female ferrets (500 g)	144	15.49	2230.56	1: 1	H5N1 [DK/35(HA226L+228S)]	Elevate to a cage

Cheng and Liao (2013), Hao et al. (2019), Qian et al. (2009), Sze To and Chao (2010), Zhang et al. (2013)

the exposure time, in the analogous 1 experiment, for the human interaction infection process, Cheng and Liao (2013) calculated that the quanta release ranged from 1023.96 to 3141.84 quanta, Qian et al. (2009) calculated the range of quanta release to vary from 992.94 to 3871.26 quanta, while the corresponding Hao et al. (2019)'s animal analogous experiment quanta release was 2861.52 quanta; in the analogous 2 experiment, Sze To and Chao (2010) and Zhang et al. (2013) calculated quanta releases of 1714.95 and 2230.56 quanta for the human interaction infection process and the animal experiment, respectively. Therefore, the reasons for the discrepancy will be analyzed in the next section.

Analogous strengths and differences analysis

Compared with previous studies, this paper breaks the traditional model that only animal experiments are used to achieve research purposes in medicine, or that only models are used to speculate in predicting human infectious diseases in the field of public defenders, and expands the application of models, and puts forward a new idea that animal infections can be simulated by interpersonal communication under certain conditions.

Many influencing factors are implicitly considered inside the Wells-Riley model commonly used in the assessment of respiratory virus transmission risk, and the indicators extracted and defined from it R_L, not only to facilitate the assessment of airflow tissue distribution in the room, but also provide recommendations for parameters that draw on the animal experimental process, solving the problem of comparative data extraction when using complex interpersonal infection processes to study the interpersonal transmission power of viruses in difficulties.

Habitat environment space is larger, the human activity range is larger, and human communicative behavior is more complex, because the influence of coupling factors cannot completely restrict the human behavior trajectory; as shown in Fig. 2, they need to be based on the nature of the limited space and the degree of interpersonal relationships, to determine whether there is direct contact transmission of limbs or just the existence of aerosol transmission mode of the problem. Therefore, if the direct use of interpersonal processes to carry out research with great uncertainty, relative to animal experiments, animal activity trajectory because of the partition of the iron cage is constrained, contact mode and distance with a certain degree of certainty, relative to interpersonal processes more certain, but analogous experiments are not strictly controlled for a single variable control test, cannot guarantee that the two analogous indicators of spatial occupancy ratio and R_L exactly equal, still in some variation within a reasonable range.

The analogous index R_L taken in this paper varies in the range of 1 ~ 2, while there is still great scope for research on the range of values of the index R_L. If the value of the index R_L is too large due to too small a Q in the denominator, the indoor exhaust system may not be fully energy efficient or the natural ventilation may be insufficient, and if the value of the index R_L is too small due to an I in the numerator, i.e., too few sources of infection, it may lead to virus; the steady-state Wells-Riley model used in this paper only applies to well-mixed indoor air, which may affect the assessment of the risk of airborne infection (Zhang and Lin 2021).

By analyzing the process of human interaction and animal experimental conditions, the infection rate is small relative to animal experiments due to the large base of susceptible population during human interaction infection; as shown in Table 4, the number of susceptible humans is tens of times higher than animal experiments; meanwhile, even for viruses with similar R0 values, HINI, H3N2, type B, p-H1N1, H9N2, and H5N1 have R0 roughly in the range of 0.6 ~ 1.2; influenza has R0 values of 2 ~ 3; SASR is slightly higher varying in the range of 2 ~ 5, and fluctuations in quanta exist depending on the virus species and differences in virus characteristics.

Conclusion

Based on the similarities that exist between the interpersonal process and animal experiments, an analogous model was developed using the principles of the Wells-Riley model with the help of the phenomena and features in animal experiments to explore the factors in the interpersonal process that may affect the calculation of quanta and thus the accuracy of virus transmission force prediction. The following conclusions were obtained:

- It was found through literature evidence that in animal experiments, because of the rigor and practicality often considered in animal medical experiments, there is similarity between the animal experimental environment and the human habitat under certain important reference indicators, similarity in physiological parameters, and similarity between the infection process in animals and the way they are exposed to the source of infection during human interactions, satisfying the conditions underlying the analogy.
- To establish an analogical model and propose reference indicators such as space occupancy ratio and indoor airflow cleanliness index that can be analogous between animal experiments and human interaction infection process when studying the influence of infection factors, and to extend the application of animal experiments by applying the Wells-Riley model to animal experiments through analogy with human interaction process
- The risk of transmission of respiratory diseases depends on many coupled and complex factors, and with the help of more definite animal experiments, the factors affecting quanta during infection are analyzed in terms of viral load of infected individuals, distance between individuals, etc., and by analogy, it is obtained that these same factors are also responsible for the differences in quanta that remain during interpersonal interactions, even when the spaces are similarly limited. The factors that need to be focused on in the process of quanta taking values to predict the power of transmission are proposed.
- The quanta during infection in animals were calculated by two sets of analogous experimental arithmetic, using an analogous model, and compared with those in human interactions, where the quanta were similar in contexts with similar modes of exposure, but also differed because of other conditions such as differences in the susceptible base and different virus species.

To sum up, the transmission of COVID-19 is affected by many factors, so this paper also has some limitations. In the process of transmission of COVID-19, there are various complicated and interdependent factors, which are rarely studied in animal experiments. In addition to the disease commonalities and individual differences that need attention, environmental personality, such as meteorological conditions, social background, and so on, there are many coupled change factors (Coccia 2020a). On the one hand, there are differences in immune system, and the affinity between different viruses and receptors of different species is different (Liu et al. 2022). Huang Y analyzed the advantages and limitations of various animal models and found that in the case of infection with SARS-CoV-2, different species also have different immune responses (Huang et al. 2022). On the other hand, the meteorological environment and the social environment, the transmission mechanism of COVID-19 is more and more inclined to air pollution to human transmission of this way; more studies focus on airborne virus infectivity (Coccia 2020b). More than 36% of studies have found that infectivity is directly or indirectly related to the indoor and outdoor environment (Rahimi et al. 2021). There are even many social, institutional, and environmental factors that support the spread of infection in the epidemic, such as the influence of different social environments such as population mobility, population density, economic vitality, and social policies. More difficult to consider in animal experiments, the high level of international trade among countries can explain the accelerated transmission dynamics and negative impacts of the COVID-19 pandemic, as trade generates a high level of socio-economic interaction between people and thus leads to the spread of viral agents (Coccia 2022).

However, studies have shown that highly stringent containment policies are not the best option to effectively reduce infections and deaths and will not only generate huge social and economic costs, but also lead to an acceleration of the transmission dynamics and cycle of the COVID-19 pandemic caused by socio-economic and environmental factors (Coccia 2020b). Therefore, in the future, appropriate preventive policies such as checking medical conditions, environmental treatment measures and some social distancing, personal protective equipment, and restrictive testing should be set up in countries to protect people's health (Sarkodie and Owusu 2020) to provide data support for further research on the spread of the virus. At the same time, future studies should focus on the control of a single factor or dimensionless parameter indicator variables used in this paper, and cleverly use the analogy idea proposed in this paper to evaluate the effectiveness of multiple impact factors on epidemic prevention and control. To further understand the dynamics of the pandemic, prevent the large-scale spread of the epidemic and national policy to provide reference.

In this paper, by revealing the common laws and individuality of animal experiments and human interaction processes, we point out the influence of factors such as viral load of infected individuals and distance between individuals on the calculation of quanta values using the Wells-Riley model, using the controllability value of animal experiments commonly used in medicine to provide a reference for the value of quanta when predicting infection rates, and to provide scientific speculation of limited space infection rate to provide reference ideas, which is beneficial to the speculation of virus transmission force under similar finite space, and to precisely guide the implementation of relevant prevention and control strategies. It provides reference indicators for environmental governance under the COVID-19 epidemic, guidance for healthy interpersonal communication and human behavior, and some references for accurately judging the spreading trend of the epidemic and dealing with the epidemic.

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Author contribution All the authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Yuxuan Liao, Shurui Guo, and Li Ying. The first draft of the manuscript was written by Yuxuan Liao, and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

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Data and material availability All data generated or analyzed during this study are included in this article. We would like to declare that the work described was original research that has not been published previously and is not under consideration for publication elsewhere, in whole or in part.

Declarations

Ethics approval Not applicable.

Consent to participate All the authors of the article agree to participate in the journal submission.

Consent for publication All the authors listed have approved the manuscript that is enclosed.

Conflict of interest The authors declare no competing interests.

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