The Eurasia Proceedings of Health, Environment and Life Sciences (EPHELS)
ISSN: 2791-8033

The Eurasia Proceedings of Health, Environment and Life Sciences (EPHELS), 2022

Volume 5, Pages 40-47

ICMeHeLS 2022: International Conference on Medical, Health and Life Sciences

# Sars-Cov-2 Virus Pathogenicity in Syrian Hamsters at Different Routes of Inoculation

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**Abstract:** In early December 2019, humanity faced a new problem caused by a coronavirus. An epidemic event capable of causing severe primary viral pneumonia in humans began to develop in the central Chinese province of Hubei. The isolated etiological agent was identified as a member of *Coronaviridae*. Currently, the global pandemic associated with a new coronavirus infection of acute respiratory syndrome type 2 (SARS-CoV-

2 - Severe acute respiratory syndrome 2) has become a challenge for humanity. In this work, the replicative capacity and pathogenesis of the SARS-CoV-2 virus in hamsters under different infection methods was evaluated. SARS-CoV-2 virus isolates showed effective replication in hamster lungs, leading to pathological lung lesions upon intranasal infection. When infected with this virus, the clinical manifestations of the disease in hamsters were characterized by decreased body temperature and live weight, moistening and ruffling of hair, and frequent stroking of the nasal mirror. In addition, SARS-CoV-2 was detected with higher titers from the group infected intranasally in cell culture from nasal, oral flushes, and lungs compared to other infection methods ($p < 0.05$). Furthermore, the pathological autopsy results showed some pathological changes in the lungs of hamsters infected intranasally. Moreover, airborne transmission was found in the co-maintenance of a healthy hamster with intranasally infected hamster. In conclusion, our work shows that the Syrian hamster model can be used to study SARS-CoV-2 pathogenesis and vaccine testing against type 2 acute respiratory syndrome.

**Keywords:** SARS-CoV-2; Pathogenicity; Biological model; Syrian hamster

## Introduction

The first members of the family *Coronaviridae* were discovered in the first half of the last century (Schalk et al., 1931, Almeida et al., 1968). This virus posed a serious problem in veterinary medicine, but the scientific community did not consider epidemic viruses particularly dangerous. Coronaviruses became a problem in 2002 when SARS-CoV (Severe acute respiratory syndrome-related coronavirus) was detected in the human population (Lvov et al.,, 2013. Chuchalin et al., 2004, Shchelkanov et al., 2013, WHO, 31 December 2003). The natural reservoir of this virus was bats (Chiroptera, Microchiroptera) (Lvov et al.,, 2013. Li et al., 2005, Menachery et al., 2015) excreting the virus in saliva, urine, and feces (Shchelkanov et al., 2020). These infect small mammals, widely used as food in Southeast Asian countries (Shchelkanov et al., 2020). The epidemic caused by SARS-CoV had a worldwide case fatality rate of 9.6% (Lvov et al.,, 2013. Chuchalin et al., 2004, Shchelkanov et al., 2013, WHO, 31 December 2003, Ed. A.G. Chuchalin, 2016).

In early December 2019, humanity faced a new problem caused by the coronavirus. An epidemic event began to develop in the middle Hubei Province of China, causing severe primary viral pneumonia in humans (Ryu et al., 2020). The isolated etiological agent was identified as a member of *Coronaviridae* (Wu et al., 2020). The genome of this agent turned out to be homologous to MERS-CoV (50%), SARS-CoV (79%), and BtRsCoV (88%). Subsequently, considering the peculiarities of genome structure, it was given a name of SARS-CoV-2 (severe acute respiratory syndrome 2) (Shchelkanov et al., 2020, CSGICTV, 2020). This virus causes infectious disease COVID-19. Clinical manifestation of the virus is rather wide.

The disease has now spread to all countries worldwide and is a global pandemic with a high fatality rate. The pandemic causes enormous damage to global health and the economy (Li et al., 2020, Wu, Z. et al., 2020, Wu, J. T. et al., 2020). At this time, vaccines against type 2 coronavirus infection are being actively developed worldwide (WHO, 26 January 2021). Preclinical vaccine trials require a suitable biological animal model to provide consistent and reproducible results (Sia et al., 2020). The ideal animal model should reflect the clinical features, viral replication, and pathology observed in humans. The presence and distribution of viral receptors should be the same as in humans. The virus must replicate in selected animal species, and there must be a correlation between the viral titer and disease severity (Bolles et al., 2011).

The method of infection of a biological model is an important factor when studying the pathogenicity of a virus. Considering the tropism of the SARS-Cov-2 virus, which may result in a more accurate elucidation of pathogenesis in a potential biological model. Following a detailed reading of the literature, in this work, we made the decision to use a hamster animal model. Hamsters had been used to study SARS-CoV, and replication maintenance in hamsters with type I coronavirus infection has been reported (Roberts et al., 2008, 2005). Also, earlier studies on SARS-CoV-2 have shown (Sia et al., 2020) that the virus under study can replicate in the lungs of an animal with a high titer.

## Method

*Isolation of Virus*

We used epidemic strain "SARS-CoV-2/KZ_Almaty/04.2020" (GenBank #: MZ379258.1) of COVID-19 virus isolated from clinical specimen deposited in the republican depository of microorganisms' collection of Research Institute for Biological Safety Problems (RIBSP) of the Ministry of Education and Science of the Republic of Kazakhstan (Patent # 34762). The virus was isolated in Vero cell culture, 4-passage. The virus titer was 4.50±0.08 lg TCID50/ml.

*Animal models*

The 16 heads of Syrian hamsters were used in the experiment. Before the work, all animals underwent thermometry, after which blood serums were sampled from all animals to determine viral neutralizing antibodies in the organisms against the studied virus, and then they were divided into 4 groups by randomized method: 1) group – (n=4); it is left as a control group. 2) group (intranasal, n=4); The second group was infected by 0.2 ml via nostrils (intranasal route); 3) group (intravenous, n=4); virus suspension was administered to animals intravenously (via a hypoglossal vein) by 0.2 ml. 4) group (subcutaneous, n=4); subcutaneous (s/c) infection of hamsters was carried out by inoculation of a virus suspension in the top of shoulder, using the same doses and volumes of preparations, as at intranasal infection. At infection of hamsters, the virus titer has made $10^{4.50\pm0.08}$ $TCID_{50}$/ml; and it was applied in an integral kind without additional dilution. After challenge, the animals were placed in cages and left in independently ventilated case for keeping animals. The animals were supervised, paying attention on their physiological condition. During the experience on 3, 5, 7, 9, 12 and 14 days after challenge, we carried out with all animals the blood sampling, nasal and oral swabs for virus isolation.

*RNA isolation.*

RNA was extracted from pathological materials using a QIAamp viral RNA mini kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions.

*Viral RNA analysis*

The following primers and probes were used to amplify the N gene of the SARS-CoV-2 virus: N_Sarbeco_F (cacattggcacccgcaatc), N_Sarbeco_R (gaggaacgagaaggcttg), and N_Sarbeco_P (fam-acttcctcaaggaacaacattgcca-bbq) (Corman et al., 2020). The viral genome was evaluated by quantitative real-time PCR using the Superscript® III Platinum One-Step RT-PCR System with Platinum™ Taq DNA Polymerase System (Invitrogen, USA) according to the manufacturer's instructions. The reactions were performed in a Rotor-Gene 6000 Series thermal cycler (Qiagen, Germany).

*Histological examination*

For microscopic analysis, lung tissue samples were taken from all studied animals and fixed in a 10% neutral formalin solution. Tissue pieces were left in formalin overnight at room temperature, then processed according to the standard procedure of histological technique (dehydration, clarification, and compaction). Tissue sections of 4–5 μm thickness were prepared from paraffin blocks using a sled microtome. Histological sections were stained with hematoxylin and eosin for general review.

*Virus isolation in cell culture*

The prepared 20% suspension of 0.5 ml was applied to the Vero cell culture monolayer after removing the nutrient medium and incubated for 60 min at 37°C. The inoculum was then removed, the monolayer was washed in three shifts with PBS solution, DMEM maintenance medium with fetal blood serum was added, and cultivation was continued at 37°C with daily microscopy of the cell culture monolayer. The presence of the virus was determined by the cytopathogenic effect in the infected cell cultures compared to the control uninfected cell culture.

*Statistical processing of experimental data*.

All studies were performed with several replications, ensuring reliable results. The results of the study were processed mathematically. The arithmetic means (X) and mean square error (m) were calculated using GraphPad Prism8. The significance of differences between the indicators ($P<0.05$) was determined using Student's test.

## Results and Discussion

Clinical signs at intranasal infection were bright expressed, that demonstrated in the general depression, frequent stroking of a nasal pocket mirror and decrease in temperature at hamsters. As well, the outcome lethality has made 20 % from the general number of hamsters of this group. In research spent by us with hamsters we also tried to define possibility of transfer of the virus from the infected to a healthy hamster by airborne infection.

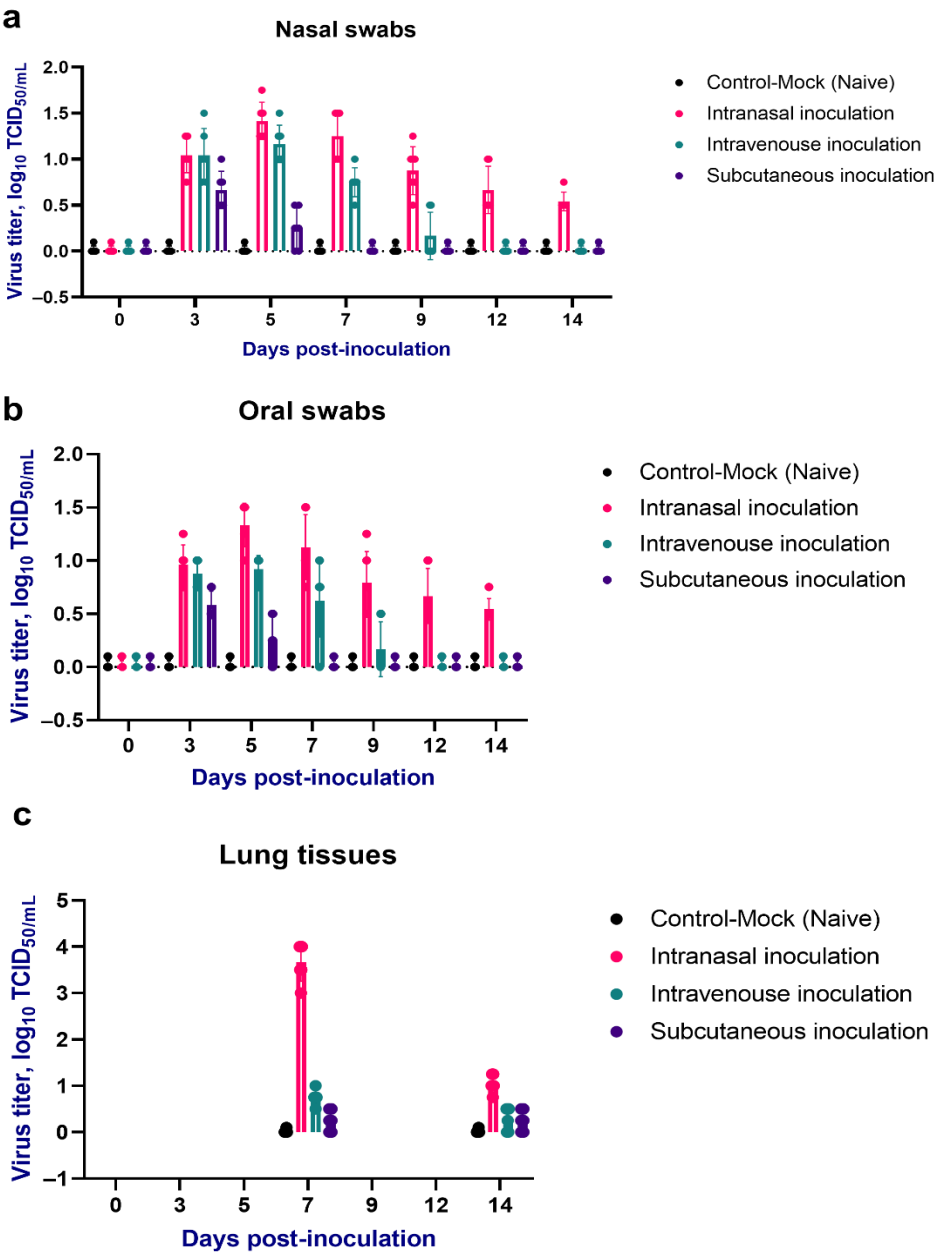


Figure 1. Viruses are released from clinical and pathological materials from hamsters infected with the SARS-CoV-2 virus by different methods. a - nasal washes; b - oral washes; c - lung tissue of infected hamsters. x - no samples were taken. ns - no significant difference; ** - $p \leq 0.002$; **** - $p \leq 0.0001$.

At this, to reveal the infection by the virus, during the joint keeping of the animals, one hamster was placed from the control group to the group infected with intranasal method instead of the dead hamster. In the result of this it was revealed, that the general clinical symptoms were found out in healthy animals, such as appetite loss, frequent stroking of nostrils, an itch, a rash, a diarrhea and temperature decrease. The researches carried out by us on study the mechanism of the virus transfer at the joint maintenance of the non-infected animal together with the infected one have confirmed the results of similar researches of other authors (Lvov et al., 2013). The body temperature control of hamsters demonstrated decrease in temperature in the group infected by the intranasal method. Also because of the shown clinical signs as loss of appetite group of the hamsters infected with intranasal method showed in measurement the constant loss of a body live weight. Group of the infected intravenously hamsters also showed irrelevant decrease in weight of a body (from $P \leq 0.02$ to $P < 0.001$ in comparison with the control group), that can testify of efficiency of infection by the intranasal method. To study the pathogenicity of a virus on internal bodies we made the postmortem opening in which we revealed dot hemorrhages and increase bronchial and well lymph nodes.

The obtained data testify occurrence of pathological changes at intranasal infection. Opening the chest cavity at intravenous inoculation showed an inflammatory process in the lungs. No such pathological changes were observed during subcutaneous inoculation. These pathological changes were confirmed by histological studies. Results of our histologic analysis demonstrated in the intranasally infected group a pathology in the form of alveolar damages, desquamation of atypical pneumocystis. Intensive coloring of microstructures, signs of sharp respiratory distress syndrome were observed. In the infected intravenously group the pathology histologic lung changes were characteristic to damages of an initial exudative phase of a sharp respiratory distress syndrome, changes are insignificant. Cuts of materials taken of the subcutaneous infected group and the control group of the pathology have not been shown.

In our work we, using one of methods of the modern molecular-genetic analysis made PCR on revealing virus RNA in samples of the received experimental animals. PCR in real time at detection virus RNA in samples of nasal and oral swabs showed results with 3 for 14 days, and also in fabrics of lungs selected on the 7th and 14th days. Received PCR results specifies on successful replication of the virus on the given models in experiment.

As well in experiment, we used virus shedding in culture of cells. We carried out the experiences on allocation of a virus from clinical and pathological materials from the experimentally infected animals in the manner of infection in culture of Vero cells. The virus shedding from clinical samples of lungs of hamsters showed at intranasal infection method for 7 days the content of a virus with titer of 3.66±0.41 lg TCID50/ml, the subsequent sample for the 14th day, the analysis revealed the virus already with smaller titer equal to 1.04±0.19 lg TCID50/ml. The intravenously infected hamsters also showed virus shedding in lungs for the 7th day with low titer 0.75±0.15 lg TCID50/ml in comparison with the group, infected by the intranasal method ($p \leq 0.0001$), and for the 14th day, the titer was equal to 0.29±0.24 lg TCID50/ml ($p \leq 0.0001$).

Hamsters from the group infected subcutaneous also showed virus shedding with low titer of 0.25±0.22 lg for the 7th and 14th days. The given value gives the chance to understand better the pathological picture at a special method of infection.

## Conclusion

By the results of the researches which we have carried out, it has been established, that hamsters are susceptible to SARS-CoV-2 virus, and have manifested development of a pneumonia similar to the people's one at infection with the given virus. Among three tested methods of infection it is revealed, that intranasal introduction with good probability cause the coronavirus infection in hamsters, than other methods. This, in its turn, confirms that the virus quickly replicates in the respiratory tract cells. Clinical manifestations of the disease were also pronounced in hamsters infected with the intranasal method, at this low mortality among infected hamsters was shown. Airborne transmission of the virus has been proven, when an infected hamster is kept in contact with healthy animals from the control group. The obtained results confirm that hamsters can be useful in creating a biological model for estimation of candidate vaccines for COVID19 coronavirus infection, since the picture of pathogenesis and clinical manifestations in this animal is close to the manifestation of the virus in humans.

## Scientific Ethics Declaration

*The author declares that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the author.

*The animal study was reviewed and approved by the Committee on the Ethics of Animal Experiments of the Research Institute for Biological safety problems of the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan (permit nos. KZ0520/013 and KZ1120/014).

## Conflict of Interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

## Acknowledgment

The authors express their gratitude to Sultankulova KT for her assistance in conducting the PCR study.

## Funding

This work was carried out within the framework of the scientific and technical program on the topic: “Development of a vaccine against COVID-19 coronavirus infection” (ITN No. 64356/PTF-MES-RK-RL-20) under targeted funding for 2020–2022 with the support of the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan.

## Acknowledgements or Notes

This article was presented as an oral presentation at the International Conference on Medical, Health and Life Sciences ( www.icmehels.net ) conference held in Baku/Azerbaijan on July 01-04, 2022.

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**To cite this article:**

Tuyskanova, M., Zhugunissov, K., Ozaslan, M., Nakhanov, A., Zakarya, K., Azanbekova , M., Kenzhebaeva, M., Omurtay, A., Dzhapasheva, A., Mambetaliyev, M. Tabys, S., Myrzakhmetova, B., & Kutumbetov, L. (2022). Sars-Cov-2 virus pathogenicity in Syrian Hamsters at different routes of inoculation. *The Eurasia Proceedings of Health, Environment and Life Sciences (EPHELS), 5*, 40-47.