JOURNAL OF MICROBIOLOGY, EPIDEMIOLOGY AND IMMUNOBIOLOGY. 2025; 102(3)
DOI: https://doi.org/10.36233/0372-9311-628
ORIGINAL RESEARCHES

REVIEWS

Review
https://doi.org/10.36233/0372-9311-628

Organoid (3D-cell) cultures in the assessment of cross-species virus transmission

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Abstract

The **aim** of this review is to characterize the possibilities of using organoid (3D-cell) cultures to assess the ability of viruses for cross-species transmission.

Sources from Web of Science, PubMed, Scopus, Elsevier, Google Scholar, and eLIBRARY.RU databases as of February 2025 were used.

In addition to classical methods of epidemiologic diagnostics and surveillance of viral infections, molecular genetic technologies (polymerase chain reaction and sequencing) are widely used in the epidemiologic surveillance system. As the best world experience shows, the use of organoid (3D-cell) cultures is promising in addressing these issues. This review analyzes data on the use of organoid (3D-cell) cultures of human and animal origin to study immunopathogenesis, as well as to assess the ability of a number of viruses (SARS-CoV-2, influenza, Zika, measles, etc.) for cross-species transmission, which determines their pandemic potential

Keywords: *review, organoid (3D-cell) cultures, viruses, cross-species transmission, epidemiology*

Funding source. This study was not supported by any external sources of funding. The work was carried out within the framework of the State assignment of G.P. Somov Institute of Epidemiology and Microbiology, No. 141-00089-21-00 for 2021-2025.

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

For citation: Kuznetsova T.A., Galkina I.V., Krizshanovsky S.P., Shchelkanov M.Yu. Organoid (3D-cell) cultures in the assessment of cross-species virus transmission. *Journal of microbiology, epidemiology and immunobiology.* 2025;102(3):370–380.
DOI: https://doi.org/10.36233/0372-9311-628
EDN: https://www.elibrary.ru/SMVGQJ

Научный обзор
https://doi.org/10.36233/0372-9311-628

Органоидные (3D-клеточные) культуры в оценке способности вирусов к межвидовым переходам

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Аннотация

Цель обзора — охарактеризовать возможности применения органоидных (3D-клеточных) культур для оценки способности вирусов к межвидовым переходам.

Использованы источники из баз данных Web of Science, PubMed, Scopus, Elsevier, Google Scholar и eLIBRARY.RU по состоянию на февраль 2025 г.
В работе системы эпидемиологического надзора, помимо классических методов эпидемиологической диагностики и надзора за вирусными инфекциями, широко применяются молекулярно-генетические технологии (полимеразная цепная реакция и секвенирование). Как показывает передовой мировой опыт, в решении этих вопросов перспективным является использование органоидных (3D-клеточных) культур. В настоящем обзоре проанализированы данные по применению органоидных (3D-клеточных) культур человеческого и животного происхождения для изучения иммунопатогенеза, а также оценки способности ряда вирусов (SARS-CoV-2, гриппа, Зика, кори и др.) к межвидовым переходам, что обусловливает их пандемический потенциал.

Ключевые слова: *обзор, органоидные (3D-клеточные) культуры, вирусы, межвидовые переходы, эпидемиология*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования. Работа выполнена в рамках Государственного задания НИИ эпидемиологии и микробиологии им. Г.П. Сомова Роспотребнадзора № 141-00089-21-00 на 2021–2025 гг.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Для цитирования: Кузнецова Т.А., Галкина И.В., Крыжановский С.П., Щелканов М.Ю. Органные (3D-клеточные) культуры в системе эпидемиологического надзора за вирусными инфекциями. *Журнал микробиологии, эпидемиологии и иммунобиологии.* 2025;102(3):370–380.
DOI: https://doi.org/10.36233/0372-9311-628
EDN: https://www.elibrary.ru/SMVGQJ

Introduction

In order to successfully carry out the tasks that ensure sanitary and epidemiological well-being of the population, the activities of the Russian network of specialized institutions in the field of epidemiological surveillance must be improved upon, which involves a system of comprehensive surveillance of the epidemic process of a particular disease in dynamics in a certain territory in order to improve the effectiveness of preventive and anti-epidemic measures [1].

The COVID-19 pandemic, etiologically associated with SARS-CoV-2 (severe acute respiratory syndrome coronavirus type 2) (Nidovirales: Coronaviridae, *Betacoronavirus*, *Sarbecovirus* subgenus), on the one hand, demonstrated the predictive capabilities of epidemiologic methods (local specialists had warned about the pandemic potential of coronaviruses several years before the pandemic [2-4]), and on the other hand, contributed to the formation of new approaches, the main one being genomic epidemiologic surveillance [5]. Genomic epidemiologic surveillance is currently one of the main elements of the large federal project "Sanitary Shield – Safety for Health (Prevention, Detection, Response)", which Rospotrebnadzor is implementing in the territory of the Russian Federation [6]. This project includes the construction of a network of diagnostic PCR laboratories and Sequencing Centers equipped with modern highly efficient NGS sequencers [5, 7]. The obtained data are aggregated by the Russian genetic data platform VGARus [5]. However, along with molecular genetic methods of research, classical methods of epidemiologic surveillance in the field of virology, in particular cell culture approaches, also continue to be actively developed [8, 9]. At the same time, 3D-cell cultures have been utilized in response to current necessities and opportunities.

The ability of viruses for cross-species transmission is responsible for the pandemic potential of viruses [10-12]. Most pandemics are associated with viruses, which may include unidentified and potentially dangerous viruses capable of rapid evolution and transmission from one host organism to another. The emergence of new potentially dangerous viruses may be caused by climate change and the melting of polar glaciers, urbanization and wildlife trade. Due to the possibility of new epidemic outbreaks of viral diseases caused by new or mutating viruses that pose significant threats to public health, it is necessary to plan adequate preventive and anti-epidemic measures. These include the development of new experimental models for studying viruses. Predicting the ability of viruses for cross-species transmission also requires new experimental models.

The aim of this review is to characterize the current possibilities of using organoid (3D-cell) cultures to assess the ability of viruses for cross-species transmission.

The analysis included scientific literature presented in the main databases (Web of Science, PubMed, Scopus, Elsevier, Google Scholar and eLIBRARY.RU) as of February 2025.

Application of organoid (3D-cell) cultures in virology

The method of organoid (3D-cell) cultures has found wide application in virology for culturing and studying the reproduction of human and animal virus-

DOI: https://doi.org/10.36233/0372-9311-628

es, studying the mechanisms of immunopathogenesis, developing and testing antiviral drugs and vaccines [13–15]. A relatively new aspect of the use of organ cultures is the solution of several issues related to epidemiologic surveillance and monitoring for viral infections. In particular, organoid (3D-cell) cultures are used to assess the ability of viruses for cross-species transmission, which accounts for their pandemic potential.

Organoids and their variant, spheroids, are related to 3D-cell cultures. There is no single definition of organoids, but their integral characteristics are multicellularity, ability to self-organize and perform any physiological functions of an organ. Spheroids are 3D-cell cultures that form sphere-like formations during proliferation, which allows cells to grow and differentiate in several directions.

Organoids are obtained from pluripotent stem cells, including induced pluripotent stem cells and embryonic stem cells, as well as from differentiated cells or tumor tissue cells [16±18]. Protocols for obtaining organoids according to the method are divided into two large groups:

- various modifications of Lancaster's (2014) method [19], differing in terms of cultivation time and the use of differentiation inducers followed by aging in microtubes or plates [20];
- use of bioreactors or mini-bioreactors [21].

One of the approaches to creating 3D-cell models is a cell line grown on a three-dimensional gel framework, as well as a spheroid culture or an organotypic (organ) culture obtained directly by fragmenting an organ and its subsequent cultivation [18]. 3D-cell cultures occupy a more advantageous position compared to 2D-cell cultures and *in vivo* models, as they allow to reproduce the structure of real organs, control signaling pathways and edit cell genomes in an environment resembling an organism, but are deprived of a number of disadvantages of living systems. The different cell morphology in 2D-cell culture from native cells negatively affects cellular processes including proliferation, differentiation, apoptosis, gene expression. Furthermore, these cultures are tumorigenic, genetically unstable, and do not reproduce the complex intercellular interactions required to model viral infections [8, 9, 22].

The advantage of 3D-cell systems, and organoids in particular, over cell lines is the reproducibility of cell layers and tissue structure present in organs. Organoids can be cultured for longer periods, frozen and used to study physiological phenomena more realistically than is possible with cell lines. Although organoid cultures are expensive and difficult to replicate the scale of massive cell line culture systems, technologies to construct them are rapidly advancing [13–15, 23].

The structure of organoids enhances viral tropism to tissues and increases the likelihood of viral infection [14, 23]. Human organoids have become an important tool in the field of viral infections research, and have played a major role in their modeling and investigation of the molecular mechanisms underlying their pathogenesis. Only organoid systems allow us to study the actual virus-host interaction, pathogenesis of infection, treatment and prevention issues. Organoids also represent an indispensable model for cross-species testing of new viruses [14, 23, 24], as discussed below. However, in terms of virology, the use of organoids in Russia is still in its early stages.

As noted by several authors, there is an urgent necessity to use more advanced biological systems for the study of viral infections, including the assessment of the cross-species potential of anthropozoonotic viruses [12, 25].

Application of human organoid cultures to study the ability of viruses to overcome the cross-species barrier

Virus-host interactions are the main driving force behind virus evolution. The ecology of a virus can only be understood through the ecology of its actual and potential hosts [26]. Natural focal pathogens of infectious diseases are co-evolved with natural biocenoses and can circulate without human involvement [27]. If a person finds himself in the territory of a natural focus, they may become an accidental host of the pathogen, and in some cases an anthroponotic chain of its transmission may be formed [28].

A key element of the ecological plasticity of natural focal viruses is their ability to overcome cross-species barriers. This ability is most pronounced in arboviruses, which are transmitted to vertebrates by arthropod vectors [26, 28]. The ecological group of arboviruses includes, in particular, Zika virus (Amarillovirales: Flaviviridae, *Flavivirus*), which causes sporadic morbidity in Africa and Asia, and in 2015 entered South America [29]. Brain organoids have been used to study the immunopathogenesis of Zika fever and routes of transmission of this virus, as it is associated with an increased risk of neurological complications in adults and children, and also causes brain malformations in fetuses of infected pregnant women [30]. Organoid cultures are actively used to study infection pathways and mechanisms of cross-species transmission for other arboviruses: Chikungunya (Martellivirales: Togaviridae, *Alphavirus*), Japanese encephalitis (Amarillovirales: Flaviviridae, *Flavivirus*), Powassan (Amarillovirales: Flaviviridae, *Flavivirus*); Dengue (Amarillovirales: Flaviviridae, *Flavivirus*) [14, 31].

An example of the use of organoids as a suitable model for cross-species virological studies is the discovery and characterization of CD46 cellular receptors for measles virus (Mononegavirales: Paramyxoviridae, *Morbillivirus*). Using a model of human respiratory system organoids, it was found that vaccine and laboratory adapted strains of this virus use CD46 (an adhesion

molecule expressed by human nuclear cells that acts as a costimulatory factor for T-lymphocytes) as a receptor, whereas vaccine and clinical wild-type strains are incapable of using CD46 [32]. Then, another receptor for adhesion of wild-type measles virus strains, nectin-4 (nectin-4) or PVRL4 (poliovirus receptor-related 4), intensively expressed on the basolateral side of epithelial cells, was identified [33]. This discovery led to a new paradigm on how measles virus enters the respiratory tract and leaves the host, with implications for the development of preventive measures.

As for contact-transmitted viruses, the threshold for entry into the human population is lower for great ape viruses (Primates: Hominidae). Human immunodeficiency virus types 1 and 2 once evolved from monkey immunodeficiency virus (Ortervirales: Retroviridae, *Lentivirus*) [28], and the tissue tropism of these viruses is being actively studied on organoid cultures [34]. Monkeypox virus (Chitovirales: Poxviridae, *Orthopoxvirus*), which is of great concern to epidemiologists, is capable of easy transmission from primates to humans and causing epidemic outbreaks [28]. Y. Watanabe et al. (2023) used models of colon organoids and human keratinocytes derived from pluripotent cells to study the replication dynamics of this virus in the respective tissues; it was shown that the virus accumulated most intensively in keratinocytes, whose dysfunction was associated with significant mitochondrial damage [35]. The more unique the primary host of the virus is (not only genetically but also physiologically), the more difficult it is for the virus to overcome the cross-species barrier. Especially interesting in this respect are bats (*Chiroptera*), whose physiology and parasite (including virome) are very specific [36]. Bats are considered a natural reservoir for a variety of viruses, including SARS-CoV-2, Ebola virus and possibly others. In most cases, bat-borne viruses require an intermediate host for effective entry into the human population. The most famous exception to this rule is the rabies-causing lyssaviruses (Mononegavirales: Rhabdoviridae, *Lyssavirus*), which easily overcome cross-species barriers due to the versatility of the nicotinic acetylcholine receptor of nerve endings used for entry of these viruses into the target cell [28]. For this reason, organoids of the nervous system are convenient and widely used 3D-cell models to study infection pathways and mechanisms of lyssavirus cross-species transmissions [37]. For Ebolaviruses (Mononegavirales: Filoviridae, *Ebolavirus*) and Marburgviruses (Mononegavirales: Filoviridae, *Marburgvirus*) associated with hemorrhagic fevers, primates act as facultative (in some cases, direct transmission of the pathogen to humans from mammals is also possible) intermediate hosts, which have long been considered a natural reservoir of filoviruses [38]. In this case, organoids of blood vessels were effective in establishing the specific features of the pathogenesis of infection [39].

For SARS-CoV[1], which caused a major epidemic in China in 2002-2003 [3], the intermediate host was Himalayan civets (*Paguma larvata*) [40]; for MERS-CoV (Middle East respiratory syndrome coronavirus), which caused a series of epidemic outbreaks in the Arabian Peninsula and many imported cases worldwide [3], the intermediate host was one-humped dromedary camels (*Camelus dromedarius*) [40]; for pandemic SARS-CoV-2, pangolins (*Pholidota*), which are widely found in Southeast Asian markets because their derivatives are used in Oriental medicine and their meat is considered a delicacy [40, 41]. The significant epidemic potential of bat-borne coronaviruses [40] necessitates the development of organoid models to study the cross-species transmission of these viruses.

Given that influenza, Ebola, Zika and pandemic coronavirus (SARS-CoV-2) viruses have demonstrated significant public health threats, organoid cultures have found applications in better understanding the mechanisms of pathogenesis and routes of infection in these infections.

In parallel with the widespread implementation of genomic surveillance, the COVID-19 pandemic has stimulated the implementation of 3D-cell models to study the pathogen of this disease, in particular, organoid cultures of human lungs, bronchi and tonsils, liver and intestines, kidneys and blood vessels [42]. COVID-19 has been shown to be a vascular disease and cause direct damage to the endothelium [43]. The neuroinvasive potential of SARS-CoV-2 has been investigated on brain organoids [44]. The use of human intestinal enteroids in which sustained replication of SARS-CoV-2 was maintained, along with the detection of viral RNA in fecal samples and the development of gastrointestinal symptoms in some COVID-19 patients, confirmed that the gastrointestinal tract may serve as one of the routes of SARS-CoV-2 transmission in addition to airborne transmission [45]. The use of an organoid model of the human upper respiratory tract and lungs to culture SARS-CoV-2 has shown that this relevant and reliable model for coronavirus research has additional value for testing other respiratory viruses, studying immunopathogenesis, and developing therapeutic and preventive measures [42].

One of the most studied examples of a virus overcoming cross-species barriers is the influenza A virus (Articulavirales: Orthomyxoviridae, *Alphainfluenzavirus*), whose natural reservoir is birds of the aquatic-ecological complex, primarily geese (*Anseriformes*) and plovers (*Charadriiformes*) [26-28]. All variants of this virus circulating among mammals, including epidemic [46] and pandemic [47] variants, have precursors in wild bird populations.

[1] Due to the emergence of SARS-CoV-2, it is now acceptable to refer to SARS-CoV as SARS-CoV-1

DOI: https://doi.org/10.36233/0372-9311-628

Brain organoids have been used to study the pathways of infection during infection caused by influenza A virus subtypes H1N1, H3N2, H7N1, and H5N1 [14, 48]. Organoids of the human respiratory tract with ciliated epithelium have also been used to study the multiplication ability of influenza viruses and other respiratory infections [48, 49]. For example, bronchial organoids have been used to culture influenza viruses of types A (*Alphainfluenzavirus*), B (*Betainfluenzavirus*), and C (*Gammainfluenzavirus*) [50]; lung organoids have been used to culture parainfluenza viruses (Mononegavirales: Paramyxoviridae) of types 1, 3 (*Respirovirus*), 2, 4 (*Rubulavirus*) [48]. Human respiratory tract organoids containing the main types of epithelial cells of the respiratory tract have shown different degrees of infectivity of human and avian strains in influenza A modeling. This relates to virus multiplication, tropism to tissues and cytokine production on these strains [51].

Using organoid models of the respiratory tract, the receptor-binding site of hemagglutinin of strains adapted to birds was studied. It was found that this site has a high affinity for α2'-3'-sialosides, while epidemic strains have affinity for α2'-6'-sialosides; pigs (*Suidae*) contain cells with both of these types of sialosides, so natural adaptation of avian variants of the virus to human receptor specificity may occur in their organism [26, 28, 52]. The situation is complicated by the fact that the cells of the columnar epithelium in the upper parts of the human respiratory tract carry mainly α2'-6'-sialosides on their surface, and in the lower parts, they carry α2'-3'-sialosides. Therefore, during infection of each individual human organism, a gradual positive selection of viral variants with α2'-3'-specificity of the hemagglutinin receptor-binding site is possible as the infection passes from the upper respiratory tract to the bronchioles, which contributes to the development of severe (up to lethal) primary viral pneumonias [53]. In this regard, the development of organoid (3D-cell models) to study the drift of receptor specificity of influenza A virus depending on the conditions of its interaction with cells is important not only in the context of virus adaptation to the human body and to study the issues of overcoming the cross-species barrier by viruses, but also to predict the clinical consequences of the development of infection.

Animal organoid cultures in the study of viruses overcoming the cross-species barrier

According to various estimates, of the 1,500 known infectious diseases in the world, 60% are of animal origin, with about 75% of new infectious diseases being zoonotic in nature, and 25% of zoonoses occurring in domestic animals. Viruses are etiologic agents of zoonoses in about 30% of cases. Zoonotic viral infections in animals are direct evidence of the ability of viruses to overcome cross-species barriers and infect humans [41, 54, 55].

The use of animal organoids for modeling zoonotic infections opens prospects for the study of host-pathogen interactions in zoonotic viral infections [41, 56, 57]. In this aspect, in addition to molecular genetic methods, cross-species organoid cultures based on human and animal cells are of considerable interest for scientifically justified prediction of the emergence of new viral variants dangerous for humans with epidemic potential [58]. According to several researchers, the use of such organoids helps to provide a biosystem to confirm the zoonotic potential of newly emerging viruses, to effectively study the infection cycle of these viruses in different species of domestic and wild animals and the ability of viruses to cross-species transitions, including adaptation to the human body. Furthermore, the use of cross-species organoids allows the cultivation of new viruses that cannot be grown in cell lines [57, 58].

Y. Sang et al. analyzed the status and potential of cross-species organoid cultures and noted the necessity for their development to study cross-species susceptibility and investigate newly emerging zoonotic viruses in both domestic and wild animals. The authors also noted the necessity to adapt the technology of human organoid production for the development of animal organoids, and in the 1st place, based on respiratory organs [58].

Despite intensive research due to the spread of the COVID-19 pathogen and other zoonotic respiratory viruses, there have been no reports of animal respiratory or pulmonary organoids until this year, since the respiratory tract is one of the main routes for viral infection. It was not until 2025 that the development of lung organoids from bats of the *Rousettus leschenaultia* species was reported. These organoids successfully mimic the structure and morphology of the pulmonary epithelium and express human-like coronavirus entry receptors — ACE2 receptors (angiotensin-converting enzyme 2) and TMPRSS2 (transmembrane protease serine group 2). This model is very much in demand and represents a great opportunity to study infections originating from bats [59].

According to several researchers, integrating organoid cultures into epidemiological forecasting contributes to addressing questions regarding virus cross-species transmission, especially after substantial optimization of human organoid systems [24, 60, 61]. As an example of an optimized system, D. Holthaus et al. imply a harmonized cross-species organoid culture system for animal infectious disease modeling [62]. To this end, intestinal organoids derived from stem cells of four species (human, mouse, pig and chicken), which are important hosts of *Apicomplexa toxoplasma* and other protozoa as agents of zoonotic infections, were developed using the Transwell platform [62]. In this aspect, the study devoted to the cross-species analysis of the transcriptome of cells of the ileum epithelium of the mouse, bat, pig, macaque and human is also of interest,

providing information on the cellular composition of these organs and their functional purpose in 4 mammalian and human species. The results also showed that bats and humans have similar gene expression patterns, which is important for studying drug metabolism. In all likelihood, these data are also important for the design of cross-species organoids [63].

The lack of animal models is due to individual animal diversity and other problems (especially in capturing and surveying wildlife). In this aspect, organoid systems represent an excellent substitute for studying cross-species and species-specific infectivity of viruses. The maintenance and differentiation of organoids from different domestic and wild animal species requires species-specific optimization of culturing conditions. For example, the generation of mouse intestinal organoids requires conditioned media containing appropriate stem cell growth and differentiation factors, which do not yet exist for most animal species [64–66]. The problem of the difficulty of experimentally confirming susceptibility to coronavirus in most animal species, especially wild animals, has been highlighted by other researchers. They also believe that substantial optimization of human organoids will help in solving the issues of epidemiological prediction [24, 44, 60].

After obtaining a certain organoid culture of animals, it is necessary to characterize it authentically, e.g. for cell heterogeneity and lineage differentiation (gene expression), etc., in order to achieve this. Various cell markers are required for this purpose. Such markers exist for humans and mice, but are very limited in most animal species [61, 67].

Despite this, research related to animal organoids has intensified in the last 10 years [59, 66, 68–70].

Animal farms where several different animal species are kept, especially when wild animals may be in the environment, are a possible site for the emergence of new virus strains and their transmission to humans. Farm animal organoids play an important role in the study of zoonotic and reproductive diseases, not only for the improvement of agricultural production but also for public health. Intestinal organoids derived from crypts or pluripotent stem cells can serve as models for investigating the mechanisms of intercellular or pathogen-host interactions in zoonotic infections of the gastrointestinal tract, in which animals can serve as asymptomatic carriers of the disease [69, 70].

Intestinal organoids of the main species of farm animals: domestic pig (*Sus scrofa*) [71, 72], cattle (*Bos taurus*) [68, 73], sheep (*Ovis aries*) [74] and other animals have been used for successful modeling of various viral infections in animals and studying pathogen-host interaction in the intestine.

Organoids of the large and small intestine of marmosets (model nonhuman primates susceptible to gastrointestinal diseases) capable of passivation and long-term cultivation were obtained [75].

Organoid models reproducing various organs of domestic carnivores: cats (*Felis catus*) [76, 77], dogs (*Canis lupus*) [76-78] have also been obtained, since it cannot be excluded that domestic animals can be intermediate hosts in the transmission of viral infections [28, 68]. Various animal species, including domestic animals (cats, dogs, hamsters) and wild animals (lions, tigers), have been found to be infected with SARS-CoV-2 [79–81]. A large number of works are devoted to the use of animal organoids to study the pathogenesis of coronavirus infection. For example, infection of enteroids obtained from different segments of pig intestines with two types of coronavirus (*Porcine epidemic diarrhea virus* and *Transmissible gastroenteritis suum virus*) revealed the tropism of coronavirus to certain cells [71, 72]. Intestinal organoids (enteroids) of Chinese horseshoe bat (*Rhinolophus sinicus*) that reproduce intestinal epithelium and are susceptible to SARS-CoV-2 infection were obtained, in contrast to unsuccessful attempts using cell cultures [45]. Based on the results of *in silico* modeling of the molecular structure of the ACE2 receptor, the Malayan pangolin (*Manis javanica*) was the main candidate for the role of an intermediate host [82]. As noted above, organoids of bat lungs whose cells expressed ACE2 and TMPRSS2 entry receptors for coronavirus have been registered [59].

Although most studies with farm animal organoids are aimed at modeling infections, most authors agree that this cell technology holds great promise for applications in veterinary medicine, agriculture, biomedical sciences, and for assessing and predicting the ability of viruses to overcome the cross-species barrier.

Conclusion

In the practice of epidemiological surveillance of viral infections, in addition to modern molecular genetic technologies (PCR and sequencing), which are the main tools of epidemiological studies, the use of organoid (3D-cell) cultures is very relevant and promising.

The review analyzes numerous examples of the use of organoid (3D-cell) cultures of human and animal origin in modeling and studying the pathogenesis of infections caused by influenza, Zika, measles and other viruses. Special attention is given to the analysis of studies using such cultures in deciphering the pandemic of a new coronavirus infection, which made it possible to reveal the source and causes of its rapid spread around the world. The development of cross-species organoid cultures based on human and animal cells (wild and domestic) is of considerable interest in the study of the ability of viruses to overcome the cross-species barrier and adapt to the human body. Such information is necessary to build strategies to prevent and control cross-species transmission and to develop science-based interventions to prevent outbreaks. Despite intensive research, there are a number of limitations and challenges to cross-species organoid cultures. These in-

DOI: https://doi.org/10.36233/0372-9311-628

clude several design features, issues of increasing their reproducibility, species-specific optimization and standardization of culturing protocols. The question of the possibility to construct organoids by fusion of human and animal cells remains open.

Thus, organoid (3D-cell cultures) of human and animal origin represent an effective model for studying the pathogenesis of viral infections, virus-host interactions, and for solving issues related to cross-species transmission of viruses, hence, for realizing the goals and objectives of epidemiological surveillance of viral infections.

Being widely implemented in virology and microbiology laboratories, these models will contribute to the development of science-based prediction of pathogen introduction from wild and farm animals into the human population, preventive measures, effective chemoprevention and treatment strategies for patients.

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DOI: https://doi.org/10.36233/0372-9311-628

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Authors' contribution. *Kuznetsova T.A., Shchelkanov M.Yu.* — concept and design of the study development; *Kuznetsova T.A., Galkina I.V., Kryzshanovsky S.P.* — collection and processing of material; *Kuznetsova T.A.* — text writing; *Shchelkanov M.Yu.* — text editing. All authors confirm that they meet the International Committee of Medical Journal Editors criteria for authorship, made a final approval of the version to be published.

The article was submitted 11.03.2025;
accepted for publication 20.05.2025;
published 28.06.2025

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Участие авторов**:** *Кузнецова Т.А., Щелканов М.Ю.* — разработка концепции и дизайна исследования; *Кузнецова Т.А., Галкина И.В., Крыжановский С.П.* — сбор и обработка материала; *Кузнецова Т.А.* — написание текста; *Щелканов М.Ю.* — редактирование. Все авторы подтверждают соответствие своего авторства критериям Международного комитета редакторов медицинских журналов, прочли и одобрили финальную версию до публикации.

Статья поступила в редакцию 11.03.2025;
принята к публикации 20.05.2025;
опубликована 28.06.2025