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VIROLOGICAL MONITORING OF WASTEWATER AS AN ELEMENT OF SURVEILLANCE FOR EMERGENT AND RE-EMERGENT INFECTIONS

The risk of biological threats has been constantly increasing in recent years. This is due both to the adaptation of avian and animal pathogens to the human organism as a result of the expansion of the area of human activity and to the development of biotechnologies. Viruses predominate among these pathogens. Examples in recent years are the COVID-19 pandemic and the continued spread of monkeypox (MPX). The situation requires the search for objects for research that would have a high informative value and could help in assessing and predicting the spread of infections. The article analyzed and assessed the potential and importance of virological monitoring of wastewater as an element of surveillance for emergent and re-emergent infections, using the example of some of them (enterovirus infections — poliomyelitis and infection caused by enterovirus D68, COVID-19, and MPX). Monitoring of enteroviruses in wastewater is a routine practice in many countries. Poliomyelitis is subject to eradication, and its incidence is extremely low. The study of wastewater makes it possible to indirectly detect the circulation of poliovirus among people, determine its molecular genetic characteristics («wild», vaccine, vaccine-derived poliovirus), the duration of circulation, and ways of spread and take appropriate

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measures in a timely manner. Enterovirus type D68 gained relevance as a re-emergent infection starting in 2014. Large outbreaks caused by it began to be registered in the USA, Canada, and then in the European region. Previously, the virus caused minor respiratory symptoms, but now it has become the cause of severe acute respiratory disease, particularly in children, and has also acquired neurovirulent properties. Its monitoring in wastewater allows for assessing the actual intensity of the epidemic process of this infection in certain territories and in certain countries, which cannot always be done based on clinical diagnosis without an additional etiological diagnosis. During the 3 years of the pandemic, SARS-CoV-2 has taken root in the human population, but a new parasitic system continues to develop. Wastewater monitoring makes it possible to assess the intensity of the epidemic process of COVID-19, which is supported by manifest forms of infection, asymptomatic persistence of the virus, and convalescents. It also allows for analyzing the effectiveness of quarantine and other restrictive measures, detecting genetic changes in the virus and trends in the formation of new variants of the virus. Since May 2022, MPX has gone beyond the borders of endemic countries and began to spread rapidly, acquiring the character of a re-emergent infection. A variant of the pathogen (clade 3) began to evolve and became transmissible from person to person. The disease it causes began to radically differ from the previously known MRC due to changes in pathogenesis and epidemiological features. First of all, this concerns the pronounced anthroponotic characteristics of re-emergent MPX *in comparison with the zoonotic manifestations of the previously known endemic* MPX. *The article discusses the results of studies conducted in different countries on the determination of MPX virus (MPXV) nucleic acids in wastewater samples using OPG002 gene analysis of all MPXVs (G2R_G), the West African clade (G2R_WA), and virus reference genomes of MPXV of the outbreak in 2022 (G2R_NML). Thus, virological monitoring of wastewater can be used as an effective element of surveillance for most infectious diseases, in particular, emergent and re-emergent ones.*

Keywords: *virological monitoring, wastewater, poliovirus, enterovirus D68, SARS-CoV-2, monkeypox virus.*

Every year, the level of biological threats increases, which is associated with the adaptation of pathogens of birds and animals to the human organism, the acquisition of long-known pathogens by new properties that increase their epidemic and pathogenic potential, and the unprecedented possibilities of biotechnology. Such technologies make it possible to create microorganisms with new properties, which theoretically can have a dual use in the future. In addition, in connection with the escalation of russian aggression, the risks of bioterrorism continue to grow. Examples of constant vigilance regarding possible future pandemic risks are avian and swine influenza viruses (Zadorozhna et al., 2016), the current emergent infection — COVID-19, re-emergent infections — monkeypox (MPX), poliomyelitis, enterovirus infection caused by enterovirus D68 (EV-D68) (Zadorozhna et al., 2015), Ebola, etc.

The COVID-19 pandemic, caused by the emerging SARS-CoV-2 coronavirus, which began in 2020, presented new challenges to healthcare aimed at increasing the sensitivity of surveillance, which would allow for a quick assessment of the presence and level of a biothreat for prompt response. At the beginning of the complication of the epidemic situation, the indication and identification systems used to identify the virus as an etiological agent of the disease are aimed at the biological material of the patient, which is important for the verification of the diagnosis, the detection of asymptomatic cases, the determination of the duration of the pathogen persistence in the human body and the duration of the incubation period of the disease. In the future, if the virus is able to maintain its viability outside the body, i.e. in abiotic objects, or it is possible to determine its genetic material in them, appropriate methods are developed that significantly increase the effectiveness of surveillance. This is important for assessing the activity of the virus transmission mechanism or for monitoring the intensity of its circulation against the background of the formation of a new parasitic system with a gradual decrease in the pathogen virulence, the formation of a certain level of population immunity, reduction in the volume of diagnostic examinations of patients, etc. The most priority objects for such research are wastewater, where viruses get into due to their tropism to the intestinal epithelium, which makes it possible to determine not only their presence on the territory where surveillance is carried out but also to indirectly calculate the level of the population infection. In case of an insufficient level of wastewater treatment, it can be a risk factor for the further spread of infectious agents.

More than 130 different types of pathogenic viruses are released from human feces. The most important among those for which the fecal-oral transmission mechanism is characteristic are adenoviruses, astro-, calici- (especially noroviruses), enteroviruses (EV), rotaviruses, hepatitis A, and E viruses. All these intestinal viruses do not have an envelope, which significantly increases their resistance to temperature and pH fluctuations compared to enveloped viruses (Guardabassi et al., 2003). As an example, we can cite the hepatitis A virus, for which temperatures of 60 °C for 30 min or 80 °C for 10 min are insufficient for complete inactivation.

In recent years, more and more researchers have come to understand that wastewater monitoring should be considered a potential healthcare tool for many infectious diseases (Kilaru et al, 2022; Hill & Larsen, 2022; Tisza et al., 2023). Gradually, wastewater monitoring begins to be used for surveillance not only for infections with a fecal-oral transmission mechanism but also for others, for example, for influenza and other respiratory infections (coronavirus, adenovirus, metapneumovirus, respiratory syncytial virus, etc.).

Since wastewater samples usually contain the genetic material of many microorganisms, the methods of their research are constantly improving both in the direction of expanding the species spectrum to be determined and increasing the sensitivity for determining the genetic diversity of pathogens of a certain species. Currently, high-throughput sequencing technologies have great potential for genomic surveillance of microbial diversity in the environment (Sovic et al., 2022). An example is a wastewater study conducted in the United States that sought to determine the maximum number of known viruses. More than 450 pathogenic viruses were detected in 363 samples using PCR and sequencing, with 54 to 98 strains detected in a single sample. The genetic diversity of individual types of viruses was correlated with clinical monitoring data. The authors assume that some genetic variants, which were rare at the time of the study, may become more important in the future. It is also emphasized that a broad study of the SE will help to determine the dynamics of the human virome population in time and space and its evolution (Tisza et al., 2023).

One of the latest scientific events dedicated to this issue was the 9th Meeting organized by The European Commission's JRC and the Directorate-General for Emergency Preparedness and Response (Directorate-General HERA), which took place on March 15—16, 2023, in particular with the involvement of Ukrainian experts.

The **purpose** of the work was to analyze and evaluate the potential and value of virological monitoring of wastewater as an element of surveillance for some emergent and re-emergent infections (enterovirus infections, COVID-19, MPX).

In this article, we focused on the role of monitoring in wastewater pathogens of 2 enterovirus infections — poliomyelitis and enterovirus infection caused by EV-D68; a new infection for the world — COVID-19, the pandemic of which continues the 4th year; and MPX, which has been known since 1970 as an endemic zoonotic disease in African countries, and since May 2022 has spread around the world, acquiring persistent human-to-human transmission.

Enteroviruses. Examination of wastewater samples for the presence of EVs can be an example of a routine component of the surveillance information subsystem for enterovirus infections. This is primarily due to the structure of EVs, which do not have a shell, which contributes to the long-term preservation of their viability outside the human body. They have single-stranded (+) RNA, and their size is only 28—30 nm. EVs multiply in the mucous membrane of the oropharynx and intestines, so a large number of them are released with feces that enter the wastewater. At the same time, the persistence of the virus in the intestine can last up to several months after the disappearance of the infection symptoms. In general, enterovirus infections are characterized by polymorphism of clinical manifestations — from damage to the central nervous system (aseptic meningitis, meningoencephalitis, poliomyelitis-like diseases), myopericarditis, mouth, hand and foot disease, pneumonia, herpangina to acute respiratory manifestations, which does not always allow timely diagnosis in the absence of virological examination and provide anti-epidemic and preventive measures. In addition, infection with these viruses is not always accompanied by manifestations of the disease. The concentration of EVs in human feces is high, which, accordingly, determines their high concentration in wastewater as well (Lizasoain et al., 2021). In the future, after wastewater treatment, a certain proportion of EVs can retain their viability and enter the river and drinking water, causing further diseases among people. According to the WHO, 1 g of human feces can contain 10^6 enterovirus particles, and 1 liter of untreated wastewater can contain 1—1000 ones (World Health Organization, 2022).

Poliovirus. Poliomyelitis is the first enterovirus infection known to mankind. This disease and its etiological agent were included in the analysis in connection with the implementation of the Global Polio Eradication Initiative (GPEI), which began in 1988. One of the main indicators characterizing the effectiveness of poliomyelitis surveillance was the number of registered and properly examined cases of acute flaccid paralysis (AFP) per 100,000 children under 15 years of age. Depending on the state of poliomyelitis vaccine prevention in the country and the effectiveness of surveillance, this indicator should be at least 1—3. In Ukraine, starting from 2015, according to WHO recommendations, it should be at least 3. Currently, against the background of vaccine prevention, the number of cases of paralytic poliomyelitis has sharply decreased in the world, the circulation of «wild» poliovirus types 2 (PV2) and 3 (PV3) has stopped, but the importance of vaccine-derived viruses (VDPVs) is increasing. In addition, the paralytic clinical form of this infection developed only in approximately 1:200 — 1:1000 of the primary infected people even in prevaccination time, and against the background of post-vaccination population immunity, this ratio is much higher. Taking into account the above, at this stage of implementation of GPEI, the need to increase the sensitivity of surveillance increases significantly. In this regard, wastewater monitoring for EVs begins to play one of the leading roles in the surveillance system for AFP/polio.

More and more researchers emphasize the importance of wastewater as an object of virological research in the surveillance system (Lopalco, 2017; Kline et al., 2022). At the same time, much attention is paid to evaluating the efficiency and developing new methods of sampling based on the concentration of polio and other EVs from wastewater (Matrajt et al., 2018), and certain features of sampling (sampling sites, frequency, etc.) that are associated with a specific epidemic situation (World Health Organization. Department of Vaccines and Biologicals. Guidelines for environmental surveillance of poliovirus circulation (WHO/V&B/03.03). Switzerland, 2003, 19 p.).

On the example of Italy, where the inactivated polio vaccine (IPV) has been used for a long period (since 2002), it can be seen that polioviruses in wastewater are usually not detected under the condition of proper vaccination. Thus, during the study of wastewater in Naples over 2010—2014, no polioviruses were detected among 22% of EV-positive samples. Among the 140 obtained isolates, 69.3% were identified as Coxsackie, 30.7% — as Echo (Pennino et al., 2018). At the same time, in the first years after the introduction of IPV (2005—2008), 2 strains of vaccine-like PV2 and **3 —** PV3 were detected during the study of 1392 samples of wastewater in 7 Italian cities. Mutations associated with neurovirulence were detected in the 5'-non-coding region (5'NCR) of all strains, and for PV2 — also in the 143 region of VP1 (Ile>Thr). Interspecific recombination in the 3D region was identified in the second strain PV2 (Sabin 2/Sabin 1) and strain PV3 (Sabin 3/Sabin 2). The authors emphasize that wastewater monitoring can be more sensitive than surveillance for AFP in the case of hidden poliovirus circulation among the population (Battistone et al., 2014).

Starting from April-May 2016, instead of the oral trivalent poliomyelitis vaccine, the world began to use a bivalent one, from which PV2 was removed as a component that, compared to other polioviruses, is able to change its genetic properties more quickly during circulation and acquires the characteristics of VDPV (with reversion of neurovirulence). Those VDPVs that are fixed in the circulation and the genetic relationship between the isolated strains found are estimated as circulating VDPVs (cVDPVs). In this regard, the importance of the wastewater study was further increased, as it was important to observe the vaccine PV2 and to monitor VDPV2 and cVDPV2 variants prompty.

For example, according to the results of a wastewater study conducted in the cities of Jinan and Linyi (China) in 2015—2017, 96% of the samples contained EVs, in particular 74.3% — vaccine polioviruses and 90.5% — other EVs. A total of 893 EV isolates were examined. It is interesting that, based on sequencing and subsequent phylogenetic analysis of isolates, it was determined that EV E-11 as a pathogen originated in 1876 and evolved at an estimated rate of 4.63×10^{-3} nucleotide substitutions/site/year, and the Coxsackie B-5 virus emerged in 1867 and subsequently changed at a rate of 3.95×10^{-3} nucleotide substitutions/site/year (Zhao et al., 2020).

Table 1. **Distribution of cVDPVs isolated in the world from environmental objects (2016 — 09.08.2022)**

Years	cVDPVs			Total
	cVDPV1	cVDPV2	cVDPV3	
2016	0	5	0	5
2017	0	2	0	2
2018	7	65	11	83
2019	26	198	0	224
2020	9	537	1	547
2021	31	495	13	539
2022 (09.08)	63	86	34	183
Total	136	1388	59	1583

A wastewater study in Senegal detected VDPV2 in 70 samples during December 2020—2021 in 7 of 14 regions of the country. According to the results of phylogenetic analysis, the circulation of 2 clusters of this virus and its entry into the country from Guinea were determined (Faye et al, 2022).

Further studies of samples from environmental objects, mainly sewage, made it possible to identify such viruses in different countries of the world (Table 1) (European Centre for Disease Prevention and Control: Update on the polio situation in the EU/EEA and the world. 2022, 16 Aug.). According to these data, a trend of increasing circulation of cVDPVs in the environment, starting from 2018, is evident. Among the total isolates, cVDPV2 accounted for 87.7%, meaning that the removal of PV2 from the oral vaccine backfired, and the number of isolates of this genetically modified virus increased from 5 in 2016 to over 500 in 2020 and 2021.

Also, since 2021, the number of cVDPV1 and cVDPV3 has increased. It should be noted that cVDPV3 was not isolated from people at all in 2021, and only 4 strains were isolated in 2022, while 13 and 34 strains were isolated from environmental objects, respectively. As for cVDPV1, as of August 9, 2022, 16 strains were isolated from humans, and 63 strains from environmental objects.

In 2022, reports on the detection of cVDPV2 were received by the IHR Polio Emergency Committee from Israel, the United Kingdom, and the United States, that is, from those countries where the live vaccine has not been used for more than 20 years. Viruses isolated in these countries turned out to be genetically related to each other, which indicates that their international distribution over long distances occurred as a result of active migration processes. In the USA, 1 case of poliomyelitis caused by this virus was reported, while cVDPV2 was isolated from the environment in Israel and the UK (WHO: Statement of the Thirty-third Polio IHR Emergency Committee. 2022, 1 November). Later, in the USA, similar cVDPV2 strains were also identified in samples from environmental facilities. In a study of 1076 wastewater samples in Rockland County, New York, and 12 surrounding counties, VDPV2 was detected in 89 samples (8.3%) (www.who.int/emergencies/disease-outbreak-news/item/2022-DON408.; Ryerson et al, 2022). Also, VDPV2 was isolated in August 2022 from wastewater in Montreal (Quebec, Canada) (Government of Canada: Polio (poliomyelitis): Wastewater surveillance, 2022).

Since 2021, an innovative monovalent live vaccine (nOPV2) containing genetically modified PV2 has been widely used in developing countries to contain outbreaks caused by cVDPV2. This virus is theoretically more genetically stable compared to the Sebin strain (*P712 ch 2 ab* strain). However, this vaccine has not yet passed all stages of clinical trials and is intended only for emergency use. Unfortunately, despite expectations regarding the genetic stability of the new vaccine virus PV2, the circulation of cVDPV2, which is derived from this virus, has already been reported in Burundi and the Democratic Republic of the Congo (Global Polio Eradication Initiative: GPEI, 2023, March,16). These cVDPV2 viruses caused 7 cases of poliomyelitis and were also isolated from 5 samples of sewage. In this regard, wastewater monitoring is gaining even greater importance.

In Ukraine, surveillance of enterovirus infections has been carried out for about 50 years and includes an annual virological examination of more than 2,000 samples of wastewater. Vaccine strains of polioviruses can be isolated annually from these samples. Since the oral polio vaccine is still used in the country, such results are evidence of the effectiveness of virological monitoring of wastewater. Thus, during 2016—2018, 246 EV strains (1.4% of the number of tested samples), including 111 vaccine poliovirus strains, were isolated from wastewater. Using the example of 2018, it should be noted that 83 (70.3%) of the 118 strains of polioviruses isolated in Ukraine were detected precisely in the process of EV monitoring in wastewater (Zadorozhna et al., 2019). During the cVDPV2 polio outbreak in Ukraine in 2021, cVDPV2 strains were also isolated from wastewater.

Thus, EV monitoring in wastewater, as a component of surveillance for enterovirus infections, is an additional element that significantly increases the effectiveness of surveillance for AFP/poliomyelitis. This is especially important for the timely detection of the circulation of genetically reversed polioviruses that originate from vaccine viruses and the timely adoption of anti-epidemic and preventive measures, primarily those related to vaccine prophylaxis.

Enterovirus D68. EV-D68 began to gain relevance as a re-emergent virus in 2014, when large outbreaks etiologically related to it began to be registered in the USA, Canada, and then in the European region (Zadorozhna et al., 2015). The virus, which previously caused minor respiratory symptoms, began to cause severe acute respiratory disease, particularly in children and later acquired neurovirulent properties with manifestations of AFP in patients. Sewage, as in the case of other enterovirus infections, is the object of research that allows for monitoring the circulation of this virus in certain areas and evaluating the actual intensity of the epidemic process. In Israel, clinical samples from 710 hospitalized children under the age of 10 were examined in 2014 to assess the epidemic situation ahead of time. EV-D68 was detected in 7 patients (1% of those examined), while 9 out of 93 wastewater samples were positive (9.7%). The analysis of the EV-D68 VP1 gene sequence from both sewage and clinical samples showed that it belongs to clade B and is genetically related to the virus circulating in Europe and North America in 2014 (Weil et al., 2017).

Anti-epidemic measures directed against COVID-19 temporarily reduced the intensity of EV-D68 circulation.

Thus, according to surveillance data in Great Britain, at a low detection of this virus in 2020 against the background of the COVID-19 pandemic, a surge in its detection in wastewater during July — November 2021 was described, which correlated with a registered increase in the number of detections of EV-D68 in clinical samples in various European countries. The simultaneous circulation of viruses from genetic clade D and subclade B3 was also shown (Tedcastle et al., 2022), which was consistent with the trend of previous years (Howson-Wells et al., 2022). According to the results of parallel studies conducted in the same year from April to October in Israel, among patients with severe respiratory disease, EV-D68 was detected in 7% of patients. All investigated wastewater samples were positive for this virus with different viral genome copy loads. The concentration of EV-D68 in the studied samples increased from the end of May to July 2021 and sharply decreased at the beginning of August. A similar trend was observed for clinical samples. According to molecular genetic research, all viruses were derived from one branch of the B3 subtype. These results highlight the potential of wastewater monitoring as an important tool for continuous surveillance of EV-D68 and other enteroviruses (Erster et al., 2022).

Currently, the mechanisms due to which the properties of EV-D68 changed toward the appearance of neurovirulence are actively studied. It has been shown that heparan sulfate proteoglycans can be used by EV-D68 as an additional entry receptor when studied in human physiological models, but do not give advantages when infecting brain cells (Sridhar et al., 2022). Another experimental study showed that EV-D68 is neurotropic regardless of its genetic lineage and can infect both neurons and astrocytes, and neurotropism is not a newly acquired characteristic as predicted. In addition, the innate immune response was crucial for limiting the development of the disease in mice (Rosenfeld et al., 2019). In other studies, on the contrary, the potential neurotropism of EV-D68 strains isolated from 2014 in the model of SH-SY5Y neuronal cell line derived from neuroblastoma, was shown. In addition to supporting viral replication and other functional studies, this cell culture model can help identify signatures of virulence to confirm epidemiological associations between EV-D68 strains and cases of AFP and enable rapid identification of new neurotropic strains (Brown et al., 2018). Taking into account the potential of modern variants of EV-D68 for the development of AFP, the need to differentiate their etiology from polioviruses and the importance of assessing the epidemic situation of heterovirus infection caused by EV-D68, the virological study of EV-D68 itself can provide the fastest and most informative results.

SARS-CoV-2. The COVID-19 pandemic has been going on for over 3 years. Its causative agent has taken root in the human population, and a new parasitic system continues to develop. Reports on the detection of RNA of the SARS-CoV-2 virus in patient fecal samples appeared even when the virus was just beginning to spread outside China (Novel coronavirus may spread via digestive system: experts // Xinhuanet. — 2020-02-02. Electronic resource; Holshue et al., 2020). Its long-term storage in environmental facilities was also discovered (Chin et al., 2020). On the basis of these data, even in the first months of the pandemic, we suggested the existence of a fecal-oral mechanism of pathogen transmission in this infection (Zadorozhna & Vynnyk, 2020). Later, similar assumptions fromother researchers appeared (Quilliam et al., 2020). It can also be predicted that as identification methods are developed and improved, the determination of this virus in wastewater will gradually become a routine practice.

As further studies have shown, the excretion of viable SARS-CoV-2 can occur from the patient's body not only with feces/ but also with urine, with subsequent entry into sewage and river water. When studying the preservation of the viability of SARS-CoV-2 in samples of river water and wastewater at a temperature of 24 °C, it was shown that a decrease in the concentration of the virus by 1 log in unfiltered water samples occurred within 1.9 and 1.2 days, respectively, and by 2 log — within 6.4 and 4 days. In filtered samples, the duration of viability increased to 3.3 and 1.5 days and to 8.5 and 4.5 days, respectively. At 4 °C, the duration of preservation of the virus viability increased. A decrease in the concentration of the virus by 1 log in river and wastewater samples occurred in 7.7 and 5.5 days, and by 2 logs in 18.7 and 17.5 days, respectively (de Oliveira et al., 2021).

Wastewater monitoring allows one to assess the intensity of the epidemic process of COVID-19 at the expense of those sources of the pathogen that support it, namely manifest forms of infection, asymptomatic persistence of the pathogen, and convalescents in whose bodies the virus continues to persist. Also, such studies provide an opportunity to analyze the effectiveness of quarantine and other restrictive measures (Steve, 2022). In Barcelona, Spain, wastewater samples concentrated by polyethylene glycol precipitation were investigated using 5 one-step quantitative reverse transcriptase PCR (RT-qPCR) targeting polymerases (IP2 and IP4), envelope (E) and nucleoprotein region (N1 and N2) of the SARS-CoV-2 genome. The research was conducted at two treatment plants before and after the introduction of a complete lockdown. SARS-CoV-2 was detected in a sample of wastewater collected 41 days before the detection of the first case of COVID-19. Later, the spread of infection among the population was shown to be from 2% to 6%. It was calculated that for the detection of SARS-CoV-2 in wastewater, the infection rate of the population served by the two treatment plants should be 0.12% and 0.9%, respectively. Monitoring of sewage networks made it possible to identify specific so-called «hot spots» of COVID-19, which in turn allowed for quickly taking appropriate measures to mitigate the consequences (Chavarria-Miró et al., 2021).

According to the results of wastewater monitoring analysis in 26 countries, the percentage of positive samples in wastewater varied from 11.6 to 100%, and the concentration of the virus varied to 4.6×10^8 genome copies/L (Ferraro et al., 2022).

Wastewater monitoring is increasingly used not only to assess the intensity of the epidemic process of COVID-19 but also for the early detection of genetic changes in its causative agent and trends in the formation of new variants of the virus (Rothman et al., 2021). A study of wastewater in Argentina in 2021 revealed the simultaneous circulation of Gamma, Alpha, and Delta variants of the SARS-CoV-2 virus. It was also shown that when N and E genes were identified, the detection rate of the viral genome was 71.2%, while when they were determined separately, this indicator was only 43.4% and 51.5%, respectively (Masachessi et al., 2022). Studies conducted in an area with low sanitation and no centralized sewage system in the Philippines identified the most effective wastewater sampling points for follow-up, as well as single-nucleotide polymorphisms in the SARS-CoV-2 genome that correlated with those in clinical samples (Otero et al., 2022). For areas with poor sanitation, other authors recommend also examining river water samples (Aguiar-Oliveira, 2020).

The problem of researching wastewater in the sanitary systems of airlines and cruise liners deserves a separate discussion, which allows for an objective sampling of infected SARS-CoV-2 among passengers passing through airports, to determine the presence of sources of the pathogen on certain boards, as well as to trace the paths of delivery of new virus variants of one or another territory. A group of researchers from Australia, the United States, and New Zealand, which carried out such work in the first year of the pandemic, emphasized the need to increase the sensitivity of the methods used since the concentration of SARS-CoV-2 RNA in the samples often approached the limit of detection. This can lead to the risk of false-negative results (Ahmed et al., 2020). An example of the importance of this issue is the spread of SARS-CoV-2 on board the Diamond Princess cruise ship in March 2020, when 18.8% of the 3,711 people present were infected. At the same time, 54% of positive individuals had no symptomatic manifestations of infection (Yamahata & Shibata, 2020).

In the UK, in March 2022, the presence of SARS-CoV-2 RNA was detected in wastewater samples from terminals (n = 150) and aircraft (n = 32) of 3 major international airports for 1—3 weeks. All sewage samples from Heathrow and Bristol airport arrivals, and 85% of samples from Edinburgh airport, tested positive, indicating a high prevalence of COVID-19 among passengers and/or airport staff. 93% of samples collected on planes were also positive. No difference in virus prevalence was found before and after the lifting of travel restrictions due to COVID-19 (Farkas et al., 2023). According to the modeling results, under current pandemic conditions, SARS-CoV-2 would be present in wastewater from 14% of short-haul flights and 62% of long-haul flights. Although studies of aviation wastewater alone are insufficient to effectively monitor the entire transboundary spread of fecal pathogens, they could be part of an expanded strategy for monitoring public health at national borders (Jones et al., 2022).

MPX virus (MPXV). Since May 2022, MRC has gone beyond endemic countries (central and western parts of Africa) and began to spread rapidly, acquiring the character of a re-emergent infection. As of April 26, 2023, i.e. a year later, 111 countries were already involved in the epidemic process, and the number of cases reached 87,078, of which 85,610 were in non-endemic countries (116 fatal cases, fatality rate — 0.14%). At this time, 30,361 cases were registered in the USA, including 42 fatal ones (https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html.). Based on the above data, the USA accounts for 35.5% of the registered cases of MPX.

The adaptation of MPXV to the human body led to the formation of a complex parasitic system, in which a variant of the pathogen (according to various literary sources, clade IIb or clade 3) separated and began to evolve independently, which acquired transmissibility from person to person, with changes in the pathogenesis of the disease and epidemiological features, which began to fundamentally distinguish this disease from the known MPX. First of all, it concerns the pronounced anthroponotic characteristics of the disease in comparison with the zoonotic manifestations of MPX. At the same time, the lack of test systems for the diagnosis of this infection, the atypical course of the disease, and the lack of practice in its diagnosis and treatment among doctors lead to the failure to detect many cases of MPX. It is also facilitated by the stigmatizing attitude toward homosexuality in some countries, as the main risk group for current MPX is men who have sex with men (MSM).

In the process of circulation, the virus continues to change. In 2022, its dominant line was B.1. However, viruses of the A.2 line are increasingly detected (Roshdy et al., 2023). Mutational analysis between these two variants revealed an extreme predominance of GA-AA mutations, indicating the activity of human APOBEC3 cytosine deaminase in this process. The role of such mutations was not characteristic of other MPXV clades. This suggested that APOBEC3-editing may be a periodic and dominant driver of MPXV evolution during the current outbreak (Gigante et al., 2022). Other authors (Isidro et al., 2022) indicate that although the 2022 MPXV (lineage B.1) is related to the 2018—2019 cases in endemic countries, the formation of a new phylogenetic branch likely reflects continuous accelerated evolution. In-depth mutational analysis reveals the influence of host APOBEC3 on viral evolution, as well as indications of potential human adaptation to MPXV in ongoing microevolution. At the same time, genome sequencing makes it possible to track the spread and transmission of this double-stranded DNA virus, whose evolution process is probably slow.

Many researchers have reported on the expediency of wastewater research in order to increase the sensitivity of MPX surveillance and monitor the evolution of the virus. PCR detection of MPXV DNA in clinical material (skin, vesicular fluid, crusts, nasal secretions, saliva, urine, feces, semen) of infected individuals confirms the possibility of using wastewater for early detection of MPXV circulation among the population in a certain area, its intensity, and trends intensity of supervision. It is necessary to take into account certain factors that can affect the detection of MPXV in wastewater, in particular, the ways and duration of virus excretion by infected individuals, the level of infection of the relevant population, the persistence of the virus in abiotic objects, the sensitivity of the methods used, etc. (Tiwari et al., 2023). It was shown that the determined amount of MPXV DNA in wastewater samples increases in accordance with the growth of the pathogen spread (Li et al., 2022).

An example confirming the persistence of MPXV in abiotic objects is the results of experimental studies, which showed its ability to maintain viability on a metal surface for up to 30 days at 4 °C and an initial concentration of 2.72×10^5 $TCID_{50}$/mL and to be used as a protective element of bovine serum albumin or sheep's blood at 22 °C up to 10—11 days (Meister et al., 2023). In wastewater for MPXV (strain hMPXV/USA/MA001/2022), which was used in the experiment at a concentration of 10^5 plaque-forming units (PFU)/mL, the half-life (T1/2) was 5.74 days. The use of sodium hypochlorite reduced this indicator to several minutes (depending on its concentration) (Yinda et al., 2023).

Based on the estimated data that one infected person releases an average of 7.78 $\log_{10}$ copies of the MPXV genome every day and the limit of detection of genomic copies (1.0 $\log_{10}$ copies/L), it was shown that 7 infected people can be detected when examining wastewater from an average treatment plant in the USA per 100,000 population. For other countries, this indicator should be recalculated, taking into account the average level of wastewater flow per capita. The authors of this study also developed a strategy for selecting the number of PCR repeats based on the expected number of cases to optimize the informativeness of such studies (Chen & Bibby, 2022).

Currently, the number of laboratories examining wastewater for the presence of MPXV nucleic acids is increasing in the world. The results show that MPXV can be detected in wastewater based on the PCR amplification of its DNA and RNA (Sharkey et al., 2022). At the same time, both qualitative and quantitative research methods are used. The G2R_G assay targeting the OPG002 gene of all MPXVs and the G2R_WA assay targeting the OPG002 gene of West African MPHVs are used. In the Netherlands, this method made it possible to determine MPHV DNA in 42% of the investigated wastewater samples. DNA extraction on (bio)solids turned out to be more effective (de Jonge et al., 2022). Canadian researchers evaluated 3 variants of real-time qPCR for the determination of MPXV in wastewater, namely the G2R methods (G2R_WA and G2R_G) developed by the CDC in 2010, as well as their own development (G2R_NML). G2R_NML was developed using the MPX 2022 outbreak virus reference genomes. All techniques had similar detection limits and were capable of detecting the presence of MPXV in wastewater. Subsequent sequencing and analysis using a basic local nucleotide alignment search tool (BLAST) identified a significantly higher number of positive results using G2R_NML, partly due to the larger amplicon size (Mejia et al., 2022).

Studies conducted in the USA showed that the concentration of the virus in the solid phase of sewage was 10^3 times higher than in the liquid phase. During the observation period (June 19 — August 1, 2022), a positive statistically significant correlation ($p < 0.001$) was observed between MPXV DNA in wastewater solids and the frequency of reported cases (Wolfe et al., 2022).

In Spain, the frequency of MPXV DNA-positive wastewater samples from 24 treatment plants over May—-August 2022 was 17.9% with a quantitative range from 2.2×10^3 up to 8.7×10^4 DNA copies/L (Girón-Guzmán et al., 2023). In Bangkok (Thailand), during the study of sewage and non-sewage water samples by PCR with subsequent Sanger sequencing during May — August 2022, an increase in DNA concentration was determined in the dynamics from the 2nd week of June to the 1st week of July from 16.4 up to 45.92 DNA copies/mL (Wannigama et al., 2022).

Over time, the monitoring of MRHCV in wastewater was included in the routine surveillance practice of many countries and also, as for other new infections, with an optional fecal-oral mechanism of transmission of the pathogen. Technical capabilities are increasing due to the introduction of the latest techniques and their high sensitivity. Based on the obtained results, it is possible to assess the intensity of the epidemic process and its trends to provide a forecast and determine the molecular genetic features of the pathogen, in particular its evolutionary changes, etc., which helps control the infectious disease.

Conclusions. Modern laboratory capabilities make it possible to use wastewater as an object of research for human pathogenic viruses not only with a fecal-oral transmission mechanism (for example, EVs, in particular polioviruses, EV-D68) but also others that are characterized by persistence or excretion with biological body fluids. This becomes especially important for emergent and re-emergent infections when it is necessary to quickly assess the epidemic situation and take appropriate anti-epidemic and preventive measures.

Also, such monitoring is important under the conditions of implementation of pathogen eradication programs, when the disease is sporadic, and the pathogen can circulate in the human population without causing typical clinical manifestations. Monitoring of polio and other EVs in wastewater has become routine practice in many countries and is an adjunct to AFP/polio surveillance.

Virological monitoring of wastewater is of particular importance for new infections, for which surveillance is still imperfect, and the epidemic situation requires constant monitoring.

Although COVID-19 and MPX are fundamentally different in their epidemiological characteristics, and their pathogens also differ in biological properties, the feasibility and effectiveness of monitoring SARS-CoV-2 and MPXV in wastewater to assess and forecast the intensity of the epidemic process of these infections is shown, and SARS-CoV-2 — also for the timely detection of evolutionary changes of the virus.

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ВІРУСОЛОГІЧНИЙ МОНІТОРИНГ СТІЧНИХ ВОД ЯК ЕЛЕМЕНТ НАГЛЯДУ ЗА ЕМЕРДЖЕНТНИМИ ТА РЕЕМЕРДЖЕНТНИМИ ІНФЕКЦІЯМИ

Ризик біологічної небезпеки останніми роками постійно зростає. Це пов'язано з адаптацією патогенів птахів і тварин до людського організму внаслідок розширення ареалу людської діяльності та з розвитком біотехнологій. Серед таких патогенів переважають віруси. Прикладами в останні роки є пандемія COVID-19 і поширення мавпячої віспи (MPX). Ситуація вимагає пошуку об'єктів для дослідження, які мали б високе інформативне значення і могли б допомогти в оцінці та прогнозі поширення інфекцій. У статті проаналізовано та оцінено потенціал та значення вірусологічного моніторингу стічних вод як елемента нагляду за емерджентними та реемерджентними інфекціями на прикладі деяких з них (ентеровірусні інфекції — поліомієліт та інфекція, спричинена ентеровірусом типу D68, COVID-19, MPX). Моніторинг ентеровірусів у стічних водах є рутинною практикою для багатьох країн. Поліомієліт підлягає ерадикації, а його захворюваність є надзвичайно низькою. Дослідження стічних вод дозволяє опосередковано виявляти циркуляцію поліовірусу серед людей, визначати його молекулярно-генетичні характеристики («дикий», вакцинний, вакциноспоріднений вірус), тривалість циркуляції, шляхи поширення і своєчасно приймати відповідні заходи. Ентеровірус типу D68 набув актуальності як реемерджентна інфекція, починаючи з 2014 р. Викликані ним великі спалахи захворювань почали реєструватися у США, Канаді, а потім і в Європейському регіоні. Раніше вірус викликав незначні респіраторні прояви, а натепер став причиною тяжкого гострого респіраторного захворювання, зокрема у дітей, а також набув нейровірулентних властивостей. Його моніторинг у стічних водах дозволяє оцінювати дійсну інтенсивність епідемічного процесу цієї інфекції на певних територіях та в окремих країнах, що не завжди можна зробити на підставі клінічного діагнозу без додаткової етіологічної діагностики. За 3 роки пандемії вірус SARS-CoV-2 укоренився в людській популяції, але нова паразитарна система продовжує розвиватися. Моніторинг стічних вод дозволяє оцінювати інтенсивність епідемічного процесу COVID-19, який підтримується за рахунок маніфесних форм інфекції, безсимптомної персистенції вірусу та реконвалесцентів. Також він дозволяє аналізувати ефективність карантинних та інших обмежувальних заходів, виявляти генетичні зміни вірусу та тенденції формування нових його варіантів. Із травня 2022 р. MPX вийшла за межі ендемічних країн та почала швидко розповсюджуватися, набувши характеру реемерджентної інфекції. Почав еволюціонувати варіант збудника (клада 3), який набув трансмісивності від людини до людини, а хвороба, яку він викликає, почала кардинально відрізнятися від раніше відомої MPX за рахунок змін у патогенезі та епідеміологічних особливостях. Насамперед це стосується виражених антропонозних характеристик реемерджентної MPX у порівнянні із зоонозними проявами раніше відомої ендемічної MPX. У статті обговорюються результати досліджень, проведених у різних країнах, щодо визначення нуклеїнових кислот вірусу MPX (MPXV) у пробах стічної води з використанням аналізів гену OPG002 усіх MPXV (G2R_G), західно-африканської клади (G2R_WA) та еталонних геномів вірусу спалаху MPX 2022 р. (G2R_NML). Простежувалася кореляція між позитивними результатами та кількістю клінічних випадків MPX. Таким чином, вірусологічний моніторинг стічних вод може бути використаний як ефективний елемент нагляду за більшістю інфекційних хвороб, зокрема емерджентними і реемерджентними.

Ключові слова: *вірусологічний моніторинг, стічні води, поліовірус, ентеровірус типу D68, SARS-CoV-2, вірус мавпячої віспи.*