ORIGINAL ARTICLE

Recent advances on human mpox

Aliya Orassay[a], Alan Berdigaliyev[a], Darya Sadvokassova[a], Ansal Diassova[a], Amr Amin[b], Wenwen Cao[c] and Yingqiu Xie[a,*]

a *Department of Biology, School of Sciences and Humanities, Nazarbayev University, Astana, Kazakhstan,* b *Biology Department, UAE University, Al Ain, 15551, United Arab Emirates and* c *Respiratory Department, The Second Affiliated Hospital of Shandong First Medical University, Tai'an, China*

Abstract

Mpox has been a concern of public health and travel caution. Using databases of WHO, CDC, google scholar, and PubMed, we searched recent literatures and reviewed the history, genomic mutation/evolution, host cell response pathways, regulation policy, vaccine and therapy development. Recent studies showed that current mpox has many genomic mutations related to regulation by APOBEC3. Current mpox has also been suggested to be associated with sexual transmission. Vaccination should be applied and anti-mpox drug should be urgently developed. More investigations are needed to ensure outbreak prevention.

Keywords: Epidemiology, Global health, Infection, Monkeypox, Mpox, Outbreak, Sexual transmission
Original Submission: 4 August 2022; **Revised Submission:** 5 December 2022; **Accepted:** 9 December 2022
Article published online: 16 December 2022

Corresponding author.
E-mail: yingqiu.xie@nu.edu.kz

1. Introduction

Mpox virus is an Orthopoxvirus genus member which family includes cowpox, vaccinia, camelpox, and variola viruses; the latter of which is the cause of smallpox infection [1]. Mpox virion is morphologically consistent with other orthopoxviruses: 200-250 nm, with a brick-shaped structure. Mpox virus is enclosed by a lipoprotein envelope covered with tubular structures and composed of a dumbbell-shaped central region [2]. Distinct mpox virus clades have been recognized such as West African and Congo Basin (Central African) [3].

Mpox virus discovery took place in 1958 when the disease was detected in monkey colonies transported from another country (Fig. 1) [4]. In 1970, a human mpox case was identified in Congo (DRC). Thus, mpox began spreading among humans across African countries, specifically in South Sudan, the DRC, Gabon, Nigeria, Cameroon, Benin, Sierra Leone, the Central African Republic, and Liberia [5]. The first human mpox epidemic in a non-endemic country occurred in 2003 [6]. The outbreak was linked to a disease transmitted from exotic animals imported from Ghana to pet prairie dogs. In 2017, another major mpox outbreak was found in Nigeria, where more than 700 probable and confirmed cases were identified [5]. Then the spread of disease to non-endemic countries occurred during 2018-2019. Starting from May 2022, mpox infection began quickly spreading worldwide [7]. More than eighty thousand cases have been observed [8]. The timeline of the history of the mpox outbreak is illustrated in Fig. 1.

It had been seven months since the first incidence of mpox was detected in May 2022, in the United Kingdom. However, the situation does not seem to be favorable, as more than 82,021 infection incidences have already been reported, as of December 2nd, 2022, from many countries that are not considered endemic [9]. Aside from that, the number of deaths has more than 60 with more than 50 cases that are not in historically mpox endemic regions as of December 2nd, 2022 [9]. This is an unprecedented situation when the spreading of the mpox began without any relation to the originally endemic African regions. The United States as one of the top recorded cases among the list of countries affected by the virus has a high number of incidences (almost 30,000 cases) as of December 2022 [8]. Using a bioinformatics website (https://www.bioinformatics.com.cn) the distribution map of the mpox

https://doi.org/10.1016/j.nmni.2022.101066

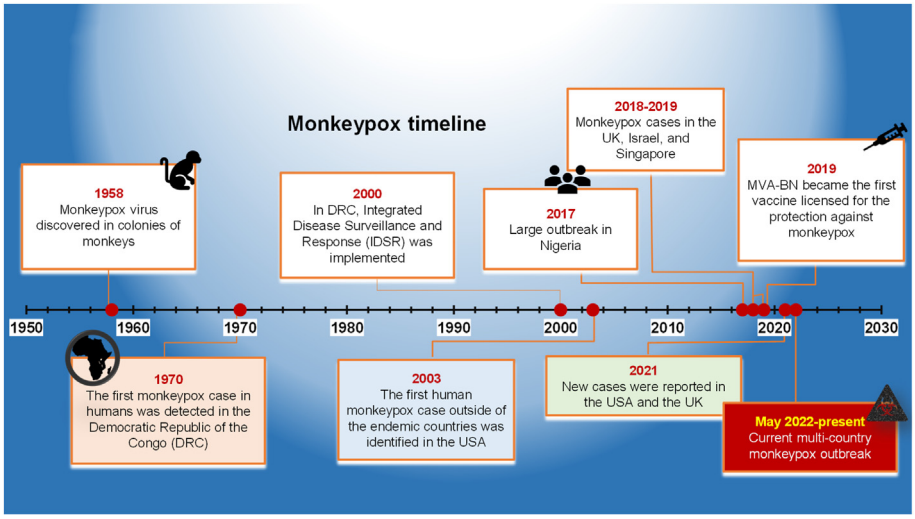

FIG. 1. Timeline of the mpox.

virus around the world (Fig. 2) was constructed. From the world map higher numbers of infected cases are observed in North America and Europe.

The worldwide situation seems to be on a moderate level of risk, but some areas are regarded as having high levels of danger. The only region considered to be low-risk is Western Pacific Region (0 to 200 cases approximately). The highest peak of the daily infection incidences appeared to be on August 12, 2022, when 1075 new virus episodes took place, meanwhile on the next day, August 13, 2022, the number decreased to 1045 which is still quite intimidating [10]. Currently, though the incidence rate has plummeted to no more than 200 cases per day, the outbreak still persists and poses a global danger [10].

Since the cause of such a severe outbreak is not yet known, as well as the cure, all countries face difficulties in restricting measures and slowing down the transmission of the infection. According to Simpson et al. [11], in general, there are some main challenges associated with mpox. First, the reservoir of the infection is unknown, as in previous cases of infection, and at present time. It is reported that the carriers of the disease are rodents, but there is no exact data on this information as, for example, in 2003 mpox was transmitted to small mammals [12]. It should also be mentioned that the causes of the outbreak in the United Kingdom, which is not an endemic country, are also unknown. Secondly, there is not enough and clear information on how the disease can be transmitted. According to Rahimi & Abadi [13], infected people did not have records of being contacted with any rodents or traveling outside of their country. This implies that the mpox virus might have acquired a new transmission route previously unknown.

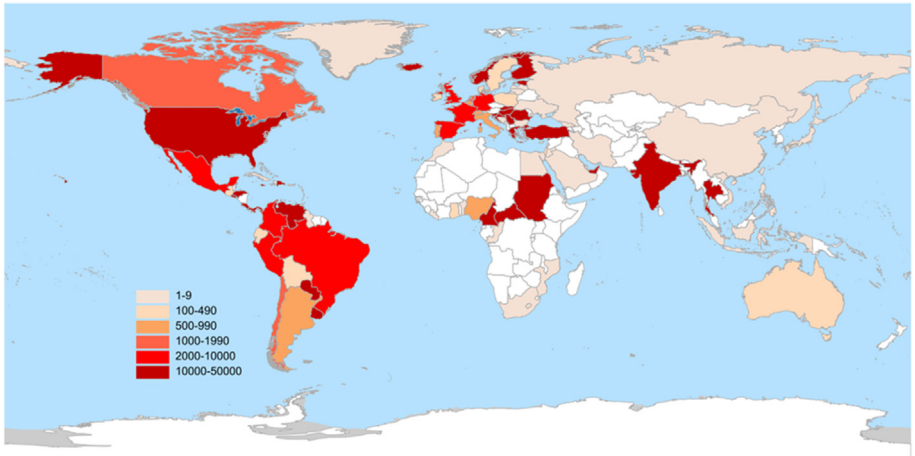

FIG. 2. World map of the case distributions. The map was generated from WHO database and online tool (https://bioinformatics.com.cn/).

Thirdly, there is no fully effective mpox medicine, since orthopoxvirus infections were declared to be destroyed as early as 1980 [14]. It is estimated that around 70 % of all people worldwide do not have immunity against orthopoxvirus species, including mpox [11]. Therefore, as a way of combatting mpox, a "ring vaccination" policy was applied in such countries as Canada, the USA, and the UK, which implies vaccination against smallpox since the latter is generic to mpox [15]. However, it is not yet known about the effectiveness of such an approach since the viruses still represent different species. Besides, the long incubation period undoubtedly affects the rate of spread of mpox [16]. Non-compliance with hygiene and preventive measures among people along with the inaccessibility of vaccines in many countries would negatively affect the outbreak situation and suggest a slow recovery from the outbreak.

2. Methods

Using keyword-searching methods, several electronic databases were used to identify recent and previous sources related to the mpox infection. PubMed is applied as a primary database to search articles and abstracts. Other databases used are Google Scholar, WHO, CDC websites, and Google. WHO database was also used to collect the data on mpox infection cases, and Bioinformatics tools (https://bioinformatics.com.cn/plot_basic_world_heatmap_015) were used for map contraction.

The most related information and literatures with different topics were acquired by the following searching with key words: mpox infection, human mpox virus, mpox outbreak, mpox mutation, the evolution of mpox infection, mpox risk factors, etc.

The recent advances and information were assured by restricting the article dates to 2000-2022, except for articles that describe the subject's past findings and are used for mpox infection outbreak timeline contractions or important biology research. Nextstrain database was used for genome sequence mutation search [17].

3. Mpox genome mutations and spreading

Data with genome sequences were reported for several currently circulating mpox strains. This includes information for 14 non-endemic countries in which the 2022 outbreak has been recorded [17]. For Portugal, 4 genomes mpox/PT0001/2022, mpox/PT0013/2022, mpox/PT0017/2022, and mpox/PT0022/2022 were accessed. Five genomes MPXV_GSTT_Patient1, MPXV_UK_2022_1-MPXV_UK_2022_4 are detected in the UK and genomes MPXV_FR_HCL0001_2022 and MPXV_FRA_2022_TLS67 were observed in France. Furthermore, in Germany, for example, genomes MPXV/Germany/2022/RKI014, and MPXV/Germany/2022/RKI025 are reported. USA genomes are MPXV_USA_2022_CA001, and MPX/human/USA/UT-UPHL-82200022/2022. Other described sequences are MPXV−CH−38134631/2022 and MPXV−CH−38156923/2022-Switzerland, MPXV_2022_NL001-Netherlands, INMI-Pt1 and MPXV_FVG-ITA_01_2022-Italy, MPX-37/Finland/2022 and MPX-42/Finland/2022-Finland, MPX/UZ_REGA_1/Belgium/2022 and MPX/UZ_REGA_2/Belgium/2022-Belgium, MPxV/VIDRL01/2022-Australia, MPXV_ISR001_2022-Israel, MPXV/ES0001/HUGTiP/2022 and MpxV/Spain/MD-HGUGM-6513479/2022-Spain, 2022/2 SLO and SLO-Slovenia. As for the genomes collected from mpox virus associated with the 2022 outbreak published, most of the mutations are point mutations. More specifically, single nucleotide substitutions are the most prevalent. In summary, and surprisingly, the most frequent mutations are resulting in more A,T than C, G.

Mutations are the major source of viral evolution. Generally, mutations impact organisms in a negative way, leading to the dysfunction of expressed proteins. However, they can also benefit viruses if the change gives rise to advantageous features. For instance, mutants can be able to reproduce more quickly and transmit between host organisms more rapidly compared to wild-type organisms. The current mpox outbreak has higher mutation rates compared to the data of previously tested Orthopoxviruses [18]. It may suggest that widespread transmission characteristically to the 2022 outbreak is related to these genetic variations. The index case of mpox associated with the 2022 outbreak was transmitted to the non-endemic country, the United Kingdom, by a British citizen who recently returned from the endemic country of mpox, Nigeria, which was tested in May [19]. Mpox virus detected in the current outbreak associated with clade has been reported [20]. The phylogenetic tree illustrating the evolutionary descent of mpox strains is available [17].

4. Transboundary risk factors, transmission, and viral microevolution

Previous studies have shown that there are several factors that might be responsible for the virus spreading. The first one is the animal-human interactions. For instance, according to CDC [21], the outbreak of infection in 2003 in the United States was related to the direct interaction of people with an infected animal, and studies from the 1980s with 338 patients demonstrated that approximately 72% of infections resulted from interaction with an animal [22]. Another factor is human

transmission. As the incubation period is approximately 17 days which is a long period, it is hard to identify the infected patient and control the contact with other people resulting in an increased number of secondary infections. Former reports showed person-to-person transmission happened among people with shared places of residents, and healthcare workers who have close contact with patients or their fomites [12]. The spread of the infection might have been progressing undetected in Europe among human transmissions caused by contacting an asymptomatic or mild symptomatic person [23].

It can also be suggested that the genomic evolution of the virus may affect its spreading. Reynolds et al. [24] state that the changes in the genomic sequence of the virus may lead to a better adaptation of the infection for different hosts or enhance the adaptation to a human host. A recent study showed that the new mpox virus genome is much different from the previous 2018-2019 strains' genome with single nucleotide polymorphism (SNPs) which is 6-12 fold more than expected [18]. This finding suggests that the current virus strain has evolved to infect people by readily proceeding through human transmission. The evolution of the virus possibly associates with APOBEC3 signaling [18]. APOBEC3 protein generally mediates resistance to the virus by generating mutations on viral genomes [25]. Based on data obtained from the experiment, it was suggested that the severity and the transmissibility among humans can be affected by the small alterations in the genome [26]. According to Hendrickson et al. [27], gene loss is considered to be a crucial factor in virus evolution by influencing virus-host interactions and leading to increased divergence because in their report, about 40 genes are missing, fragmented or truncated, in mpox virus strain of Western African or a clade with the higher pathogenicity Central African strain [27]. For example, the lost genes homologous are C3L or C16L/B22R respectively in the Western African and Central African strains [27]. However, there are some controversies [28,15]. Unlike other double-stranded DNA viruses, comparably, the mpox virus has a genome of about 196K base pairs (bp) of double-stranded DNA [29,30] and it is possible that host cells regulate the repairing of DNA mutations in the viral genome.

5. Virus entry and host cell response pathways upon virus infection

Intracellular mature viruses, as well as extracellular enveloped viruses, are virus particles that are capable of starting the new infectious cycle, and their entry into the cells is through different mechanisms [31,32]. Entry of the mpox virus, which is similar to other poxviruses, is characterized by multiple steps such as attachment, formation of fusion intermediate, pass and deposition of the nucleoprotein core of the virion in the cytoplasm [33]. The fusion of the virus is associated with pH or endocytic pathway [34,35]. After the viral entry, the process of early viral gene expression is regulated by viral RNA polymerase accompanied with early transcription factors, and synthesis of viral mRNA is regulated by early promoters [36]. Following the production of early proteins which initiate the core uncoating, DNA replication, intermediate and late transcription steps are regulated by host-derived transcription factors with late gene expression which is mainly related to structural protein, and virion assembly followed by DNA taking up, and condensation by general mechanisms [37,32,36].

Like other poxviruses, mpox is considered to be a self-sufficient DNA virus, due to its ability to encode its own DNA replication, transcription, and mRNA biogenesis machinery for replication. Despite that, it is dependent on host ribosomes to synthesize viral proteins and replicate [38]. For that reason, it is crucial to study the host cell response pathways during the mpox infection for a deeper insight into virus-host interactions and the facilitation of antiviral therapy. One study using microarray analysis of mpox virus infected macaca mulatta kidney epithelial cells identified major gene clusters which are associated with cell death, cell cycle, signaling and gene regulation upon 3 hours infection [39]. Most pathways are cancer related canonical pathways. To the surprise, many potassium, sodium channel, ion channels or transporters are found to be downregulated upon infection which suggests the host cell osmotic dysregulation even it remains elusive [39]. Moreover, the study identified a Ataxia telangiectasia mutated protein (ATM) pathway downregulation which may involve in DNA repair disruption, explaining that gene mutation may happen. Another essential pathway is ephrin receptor signaling, which might be explained by induced cell-to-cell communication or the presence of pleiotropic genes for actin polymerization or cytoskeleton organization [39]. Virus particles egress in EEV form. Cell-to-cell infection is driven by formation of actin, which is consistent with the study conducted by Realegeno and his colleagues [40]. Importantly, the study shows a dramatic copy number increase of histone-coding genes along with suppressed major transcription regulators including YY1, HDAC2, CREB1, suggesting the dependence of host histone changes and effect on viral factors [39]. Similarly, another study revealed the major group of genes affected by the infection plays a role in chromatin organization, most of which belong to the histone [41]. The induction of histone genes is attributed to de novo polyadenylation of the transcript by the virus [42,43].

It has been shown that host factors required for two clades of the mpox virus of Republic of Congo or West Africa

infection in human haploid cells include Golgi trafficking, especially vacuolar protein sorting (VPS) proteins are essential [40]. Knockout of VPS genes such as *VPS52*, showed a reduction in extracellular virus (EV) production or viral egress and an actin tail formation defect was also detected which is similar to above reports [39,40].

6. Recent findings on genomic mutation and mechanisms

The comparison analysis of genome sequence causing the current outbreak with the genome sequence of other historically present mpox viruses showed that 5' GA-to-AA is the major mutation present in the 2022 mpox virus [44]. Further validation of microevolution of the current mpox virus during person-to-person transmission was performed through phylogenomic analysis, showing the emergence of 15 SNPs with the same mutations performed by GA-to-AA and TC-to-TT replacements [18]. Those findings confirm the accelerated evolution of the mpox virus which poses the threat to humanity.

As mentioned above, recent studies revealed that APOBEC3 may serve as the cause of mpox virus evolution [18] but was originally identified to serve as the defense mechanism against infections caused by retroviruses [45]. APOBEC3 plays a significant role in altering or modifying the viral DNA by deamination but APOBEC3 proteins are not capable of editing the viral genome of *Poxviruses* [46–49]. DNA viruses are capable to avoid restriction mediated by APOBEC proteins [46,49].

7. Current new discovery of mpox-associated diseases

An outbreak in non-endemic countries has a different clinical feature from the initial representation of rash in the genital and peri-anal areas of the human body [50]. It is different from the typical historical appearance of the infection that first appears on the face, oral cavity, then may progress to the hands and feet, and further to other body parts. According to the WHO [51], clinical features of mpox suggest mpox infection tends to spread through sexual contact. For example, the high occurrence of mpox viral infection cases within non-endemic countries in a large number of men who have sex with men (MSM) suggests current mpox might be sexually transmitted by close contact [51].

Recent reports on lesions mainly appearing in the anal and genital areas suggest the possible transmission of the virus through sexual contact [52]. Even though a reported dual infection patient was prior HIV infected, how HIV associates with the mpox infection remains elusive. Nevertheless, it was proposed that progressive HIV infection is capable of causing more acute consequences of mpox infection [52]. Antiretroviral therapy that normalizes CD4+ T-cell count shows the suppression of viral load could possibly play a key role to prevent considerable outcomes of mpox infection [52]. Thus, infection with HIV significantly may enhance mpox infection, and vice versa [53]. The pattern of transmission through sexual intercourse implies the possibility of patients being co-infected with other sexually-transmitted diseases along with the mpox virus. Serological examination of 34 years old HIV-positive male patients who had sexual contact with men showed the appearance of syphilis infection and the presence of mpox infection was detected using vesicle fluid electron microscopy [54].

Another main finding is the presence of the mpox virus in seminal fluid obtained from mpox patients, even though it cannot serve the direct evidence of the virus being a sexually transmitted disease. Viral systemic dissemination and viremia might be the reasons of mpox virus appearance in semen [55]. The spread of the virus happens through direct, close contact with infectious body fluids, skin lesions, scabs and face-to-face contact via respiratory droplets produced [8]. In summary, there are several preliminary risk factors for the acquisition of infection such as sexual transmission, being HIV positive, and being previously diseases with sexually transmitted diseases such as syphilis [7].

8. Clinical features and management

The mpox infection is characterized by headache, fever, rash, and skin lesions [56]. Despite the similarity to the smallpox virus, the mpox infection has an identifiable feature and it is lymphadenopathy which is absent in smallpox [57]. Furthermore, lesions appear on the body of the infected human and their number might be up to thousands [1]. With the PCR test of the blood and upper respiratory tract swabs samples, it was managed to identify the mpox virus in the patients. For treatment, according to Adler et al. [58], oral drugs named brincidofovir and tecovirimat demonstrated their effectiveness in treatment against the mpox infection. Brincidofovir showed good results in different animal models with orthopoxvirus and mpox virus [59]. Furthermore, Hutson et al. [59] reported the increased effectiveness of the brincidofovir when it was used in combination with another drug named as TPOXX. With regard to tecovirimat, Russo et al. stated that it can be useful as it was very effective against mortality from the mpox virus in primates [60]. Further studies should be implemented in order to validate the effectiveness of the drugs as the experiments on the

animals demonstrated promising results which can be used for drug development.

9. The policy of mpox prevention and travel regulations

Despite the relatively slow-spreading and mortality of the mpox infection compared to COVID-19, the new virus should not be underestimated and precautious activities must be implemented in order to control its spreading. Currently, the situation is tolerable, and the first step in fighting against the mpox virus can be suspending or minimizing flights to the endemic countries of mpox infection. Moreover, countries should call their citizens to avoid visiting those countries. Laboratory testing is required to identify the mpox virus [61], but it might take some time. Thus, scientists need to find the fastest way of determining mpox in patients as it will prevent further spreading. As a solution, machine learning technology, specifically, a modified VGG16 model can be applied to mpox detection [62]. Sanitary measures also can contribute to the prevention of the spread of the infection. Cleaning hands, avoiding contact of mouth, nose and eyes, or contact with sick people would also be enhanced measures [16].

There are no travel-related bans and restrictions around the world. However, in case of further spread of the mpox virus, it may raise global awareness to implement prohibitions and restrictions on travel. Even though PCR testing for mpox infection is not a prerequisite for traveling, some counties have already raised a big concern about the infection. For example, the first case of mpox infection in Thailand was detected among tourists who came from Malaysia through the Kedah state border. This was the cause of concerns among the government, following the implementation of preventative measures to become the focus [20]. Thailand's Disease Control Department announced entry inspection standards and enhancement of screening for mpox infection. Special attention is given to travelers who have symptoms of mpox infection and come from countries or residents of countries with confirmed mpox cases [63].

10. Vaccination

Modified Vaccinia Ankara, shortened as MVA, is a smallpox vaccine that can be also used for protection against monkeypox [64]. The vaccine was modified and is now produced by the Bavarian Nordic [64]. Vaccination against mpox is already available in Canada and the USA. However, there are some concerns that scientists expressed when it comes to vaccination against mpox. One of the major concerns is the fact that the efficiency of MVA in humans under new and continue mutations [65]. Another issue arises when people think we have taken too much vaccines including flu, COVID-19 in pandemic era. However, scientific and clinical guidelines should be established to avoid the new pandemic, based on lessons we have learned from COVID-19 [66]. Thus, developing new vaccines as early as possible would be significant in current unpredictable new emerging infections which may come again [66].

11. Conclusion

Mpox as a zoonotic infection, has been spread among humans. Infection mainly takes place in the Central and Western African regions. However, current outbreaks in non-endemic countries and increasing cases of infection through human-to-human transmission are raising a huge concern around the world. For prevention of further infection spread, it is essential to conduct more comprehensive genomic studies which might give a better understanding of antiviral therapy targets. Infection management and vaccination strategies should be strictly applied to combat the mpox infection especially during traveling. In addition to vaccine development, antiviral drugs could be developed from drug bank screening based on host cell signaling pathways [67] or natural products targeting the virus based on lessons we have learned from COVID-19 [68].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Aliya Orassay: Virus entry and host cell response pathways upon monkeypox infection; Genomic analysis from previous studies; Current new discovery of monkeypox-associated diseases; Part of the policy of monkeypox infection prevention and transboundary risk factors, transmission, and viral microevolution; Introduction and conclusion, formatting. **Alan Berdigaliyev:** Transboundary risk factors, transmission, and viral microevolution; Clinical features and management; The policy of monkeypox infection prevention; Outbreak map

construction. **Darya Sadvokassova:** Current situation in non-endemic countries; Challenges of responding to monkeypox virus. **Ansal Diassova:** Monkeypox outbreak history; Travel associated spread; Timeline of monkeypox history; Vaccination. **Amr Amin:** Critical comments and revising. **Wenwen Cao:** Critical comments, consulting and revising. **Yingqiu Xie:** Supervision, supervised the project; Made outline and revised the paper; obtain funding.

Acknowledgement

We would like to thank NU FDCRGP grant (110119FD4531, and 110222021FD2920) and UAEU-AUA grant (2019,12R118). We also thank students Didar Zeitkaziyeva and Arailym Myrzagaliyeva for kind help on editing references format.

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