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Review Article

Health Emergency Preparedness and Response Authority's (HERA) role in dealing with the monkeypox emergency in the European Union

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Abstract

The current article examines and analyzes the actions taken by the European Commission, specifically through the Directorate-General Health Emergency Preparedness and Response Authority (HERA) – an organization that anticipates threats and potential health crises, through intelligence gathering and building the necessary response capacities), aimed at supporting member states in limiting the spread of MPOX (monkeypox – an infectious disease caused by the monkeypox virus). It explores specific pharmaceutical products and vaccines procured by HERA and how they have been distributed among member states. The article raises questions about the compliance in purchasing pharmaceutical products and vaccines lacking approval for use within the European Union, highlighting the potential new regulatory challenges for Bulgaria if it needs to secure medications for treatment of human smallpox disease such as Jynneos and TPOXX (Tecovirimat) for its citizens. In conclusion, the article notes the swift response of HERA through the procurement of the Jynneos vaccine and TPOXX medicinal product. This swift response may have contributed to the decline of MPOX cases in the European region, potentially due to collaborative efforts among health authorities at both European and national levels. This success underscores the importance of cooperation among health authorities at various levels in combating infectious diseases.

Keywords

antiviral medicinal products, emergency, European Union, HERA (Health Emergency Preparedness and Response Authority), human MPOX (monkeypox), vaccines

Introduction

In mid-May 2022, reports of MPOX (Monkeypox) outbreaks surfaced, with initial information indicating that health authorities in various parts of the world were reporting cases of the infection (Kasuya 2023). The infection rapidly spread across Europe, America, and subsequently across all six regions of the World Health Organization. A total of 110 countries reported approximately 87,000 infections and 112 deaths. Based on the gathered data from different parts of the world, on July 23, 2022, the World Health Organization declared the situation a Public Health Emergency of International Concern (PHEIC), alongside which the WHO released a strategic preparedness and response plan for MPOX and a set of technical guidance documents (WHO 2023a).

From a historical perspective, after 1970, sporadic MPOX epidemics emerged in Central and East Africa, and West Africa. In 2003, an epidemic in the United States was linked to one induced by imported wild animals into the country. Since 2005, thousands of presumed cases have been reported annually in the Democratic Republic of Congo. In 2017, MPOX reappeared in Nigeria and continued to spread among people throughout the (WHO 2023b).

MPOX (Monkeypox) is a viral disease caused by the monkeypox virus, a type of Orthopoxvirus. There are two different classes: Class I and Class II. Monkeypox is a viral zoonosis (a virus transmitted to humans from animals) with symptoms that are quite similar but milder compared to those observed in patients with smallpox in the past (Centers for disease control and prevention 2023). The disease is endemic in West and Central Africa and is spreading for the first time in Europe. The therapeutic goal of treating monkeypox is to manage the rash, alleviate pain, and prevent complications. Early and supportive care is crucial in managing the symptoms and avoiding further issues.

Materials and methods

A systematic review and analysis of data from various sources of information have been conducted, including articles and official announcements from the European Commission, the European Centre for Disease Prevention and Control (ECDC), the World Health Organization, and the European Medicines Agency. Additionally, articles from scientific databases such as PubMed, Elsevier, and Google Scholar were reviewed. The analysis of the data included examination of various regulatory documents at the European and national levels.

European

In the European Union, according to the European Centre for Disease Prevention and Control (ECDC) data, between May and July 2022, around 2,682 cases of monkeypox were reported in 23 EU member states (Austria, Belgium, Bulgaria, Germany, Greece, Denmark, Ireland, Spain, Italy, Latvia, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovenia, Hungary, Finland, France, Croatia, Czech Republic, and Sweden), as well as Norway and Iceland. In most of the affected individuals, skin lesions were identified around the genital area, indicating that transmission likely occurs through close physical contact during sexual activity.

Results and discussion

The ongoing 2022 mpox epidemic is affecting an increasing number of countries. There's an urgent need to update clinical presentations' characteristics as well as therapeutic guidelines for mpox to enhance efforts in controlling this global epidemic (Liu 2022). Researchers in the field emphasize that all countries worldwide should maintain their surveillance and response capacities, integrating prevention and care for MPOX into national health programs (Salvo 2023).

In response to the infection's spread among member states and with the aim of safeguarding public health, the Directorate-General "HERA" of the European Commission held discussions with member states regarding exploring options for purchasing vaccines and pharmaceuticals to be made available in connection with limiting the spread among those infected with monkeypox.

As of June 2022, the available vaccines authorized for use in the European Union and the United States are

1. Imvanex (modified vaccinia Ankara – Bavarian Nordic (MVA-BN) virus) – a vaccine initially approved through the centralized procedure of the EU, initially against smallpox, but subsequently, in July 2022, also against monkeypox (EMA 2022a).
2. JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Non-Replicating) – a vaccine against smallpox and monkeypox, authorized for use by the Food and Drug Administration (FDA) (FDA 2019).

The manufacturer of both mentioned vaccines, Jynneos and Imvanex, is the company Bavarian Nordic. According to the European Centre for Disease Prevention and Control (ECDC) assessment, affected countries are recommended to consider the possibility of early vaccination post-exposure using Bavarian Nordic's third-generation vaccine to prevent the disease or reduce its severity.

In regard to antiviral medications specifically for the treatment of the infection, there are two products authorized for use in the EU and the US

1. Tecovirimat SIGA 200 mg hard capsules (INN Tecovirimat) – authorized for use through a centralized

procedure in early 2022 (EMA 2022b). According to the approved summary of product characteristics, this medication is indicated for the treatment of various viral infections in adults and children weighing at least 13 kg, including smallpox, monkeypox, or cowpox. Treatment with Tecovirimat should commence as soon as possible after diagnosis. The recommended dosage for adult patients weighing over 40 kg is 600 mg (three capsules of 200 mg each) every 12 hours for 14 days, with the final package containing a total of 84 hard capsules.

2. The second authorized medication is TPOXX 200 mg (INN Tecovirimat), indicated for the treatment of smallpox caused by the variola virus in adults and pediatric patients weighing at least 13 kg. Based on an FDA recommendation, it is also indicated for patients with MPOX (FDA 2023).

By the end of August 2022, according to the World Health Organization (WHO), the reported cases of MPOX worldwide in week 34 (August 22nd to 28th, 2022) indicated a 13.7% increase compared to the previous week, with 6,746 newly reported cases in week 34 compared to 5,931 in week 33 (WHO 2022a, 2022b) (Fig. 1). The majority of cases in the last four weeks were reported from the Pan American (66.9%) and European regions of the WHO (32.3%). The reported information for the top ten most affected countries includes the US (17,333 cases), Spain (6,543 cases), Brazil (4,493 cases), Germany (3,455 cases), France (3,421 cases), the UK (3,340 cases), Peru (1,434 cases), Canada (1,228 cases), the Netherlands (1,160 cases), and Portugal (846 cases), representing 88.5% of all registered cases worldwide. Six of these countries are in Europe. As of August 31st, Bulgaria has confirmed four cases with laboratory results.

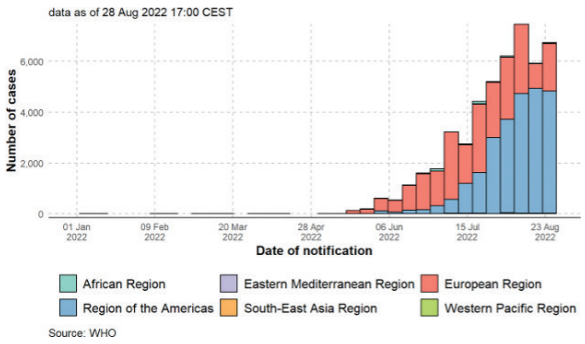

Figure 1. Distribution of cases by month (January 2022-August 2022) for the six WHO regions.

Direct purchase of vaccines from the European Commission

The European Commission, based on information received from member states and in accordance with the approved 2022 work plan of the Health Emergency Preparedness and Response Authority (HERA), conducted negotiations with Bavarian Nordic and purchased over 330,000 doses of the JYNNEOS vaccine in several stages (HERA 2022). The decision to procure doses of the vaccine approved in the United States, rather than the Imvanex vaccine, was due to Bavarian Nordic's ability to deliver JYNNEOS doses quickly, while Imvanex production would have taken longer, delaying deliveries to member states. Subsequently, the purchased doses were donated to requesting member states based on the pro-rata principle, aiming for an even distribution of doses according to each country's population. Priority was given to delivering vaccines to EU member states that had the highest number of confirmed cases at the time of the donation agreement between the respective member state and the European Commission, represented by the HERA Directorate-General. This direct procurement of the JYNNEOS vaccine sets a precedent as it marks the first instance of the EU budget being used through the EU4Health program to directly purchase vaccine doses that are later donated to member states.

The first delivery of 5,300 doses of the JYNNEOS vaccine was made on June 28, 2022, with Spain being the first country to benefit from the donation after the United States, as it was one of the most affected countries at that time (Olivier 2022). It's important to note that for a member state to receive the JYNNEOS vaccine as a donation, the respective member state must enter into a donation agreement with the European Commission and confirm that the FDA-approved vaccine can be applied within the territory of the receiving member state.

The logistics for delivery were carried out through the EU Civil Protection Mechanism, with deliveries made to the following member states: Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, and Sweden. Even quantities of the vaccine were delivered to Ukraine, Norway, and Iceland. The three countries that received the largest donations of vaccine doses were Germany, Italy, and France, which were among the most affected by the spread of MPOX.

To prevent and avoid the establishment of endemic outbreaks of MPOX in the European Union, on November 17, 2022, the signing of a Framework Agreement between Bavarian Nordic and HERA, representing the European Commission, was announced for the delivery of the vaccine. Fourteen member states participate in the Framework Agreement, allowing them to deliver up to 2 million doses of the vaccine within their territory between 2023 and 2024 (European Commission 2022a).

Delivery of an antiviral medicinal product for the specific treatment of MPOX

In response to the epidemic situation, the European Health Emergency Preparedness and Response Authority (DG HERA) negotiated with the manufacturer Meridian/SIGA. As a result of the negotiations on September 26, 2022,

10,000 therapeutic courses of the medicinal product TPOX (INN Tecovirimat) were purchased. The purchase was made through rescEU funds to treat patients in member states with immediate needs. The purchased therapeutic courses of the medicinal product are available to all Union member states participating in the European Union Civil Protection Mechanism (European Commission 2022b).

On October 23, 2023, the signing of a Framework Agreement for the delivery of the medicinal product was announced. Thirteen EU member states are participating in the Framework Agreement, with a total contract value of 18 million euros. Therefore, member states will be able to deliver specific antiviral vaccines to their citizens when needed (SIGA Therapeutics 2023).

Sharp decline in MPOX cases in Europe

From the report published on August 14, 2023, regarding the spread of MPOX across all 6 regions of the World Health Organization, a clear trend of a sharp decrease in MPOX cases is evident in the European region (Fig. 2). Besides Europe, the only other region where a decrease in MPOX cases is observed is North and South America. According to data from the European Centre for Disease Prevention and Control (ECDC), administered doses of the vaccine produced by Bavarian Nordic between September 2022 and February 2023 exceeded 333,000 across 25 countries within the European Union and the European Economic Area (European Center for Disease prevention and control 2023).

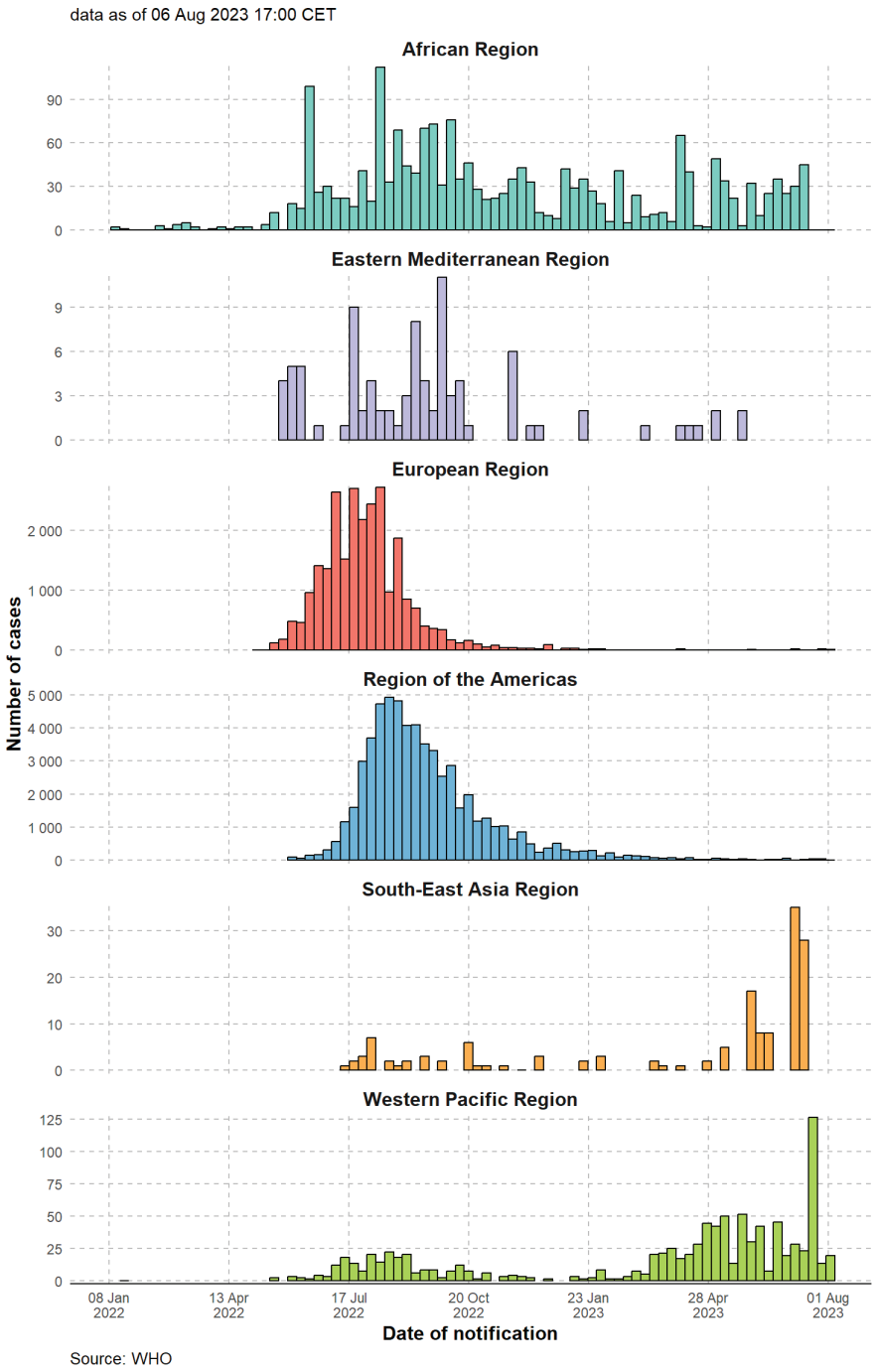

Figure 2. Distribution of cases by month (January 2022-August 2023) for the six WHO regions.

Possibility of application of Jynneos and TPOXX in Bulgaria, as well as measures taken at the national level

Alongside actions at the European level concerning preventive measures and treatment of those affected by MPOX, Bulgaria has also implemented prevention measures based on the recommendation of European health authorities. A special ordinance, Minister of Health Order No. N-5 of November 29, 2022, has been issued for the conditions and procedures for conducting diagnostics, prevention, and control of monkeypox (Ministry of Health 2022). This ordinance defines the conditions and procedures for conducting diagnostics, prevention, and control of monkeypox, including:

1. Conditions and procedures for isolation, including mandatory isolation of individuals with monkeypox.
2. Conditions and procedures for quarantine, including mandatory quarantine for contacts of individuals with monkeypox.
3. Criteria for identifying contacts of individuals with monkeypox.

Regarding therapeutic options, there remains an open question about the possibility of using the vaccine Jynneos or the medicinal product TPOXX (INN: Tecovirimat) in Bulgaria. The Law on Medicinal Products for Human Use (LMPHU) allows treatment of a specific patient with a medicinal product not approved under LMPHU, through a special order from a hospital, under conditions specified by the Minister of Health (Article 9 of LMPHU).

Additionally, the Minister of Health, upon a motivated proposal from the Chief State Health Inspector and coordinated with the Executive Director of the Executive Agency of Medicines, can authorize treatment for a specific period with a medicinal product not approved under Chapter Three of LMPHU when the country faces an epidemic caused by pathogens or toxins, or when there's presumed or confirmed distribution of chemical agents or nuclear radiation, and there's no appropriate authorized medicinal product in Bulgaria or the EU is available (Article 10 of LMPHU).

The Jynneos vaccine does not fall within the scope of Articles 9 and 10 of the Law on Medicinal Products for Human Use. These provisions allow the use of unapproved medicinal products in the country for specific patients, but **only for the purpose of treating specific diseases** and in compliance with the regulations and requirements of the secondary normative act (Ordinance No. 10 of November 17, 2011, regarding the conditions and procedures for treating unapproved medicinal products in the Republic of Bulgaria, medicinal products applied outside the conditions of the authorization for use, and compassionate use medicinal products, as well as the conditions and procedures for inclusion, changes, exclusion, and supply of medicinal products from the list under Article 266a, para. 2 of the law on medicinal products for human use). The medicinal product represents a vaccine intended not for treatment but for prophylaxis and prevention of monkeypox.

Since explicit legal provisions for the application of unauthorized medicinal products for prophylaxis are not available, the possibility remains open for discussion concerning Article 9 of the Law on Medicinal Products in Human Medicine (LMPHU), and consequently, Regulation No. 10/2011 by analogy for medicinal products used for prophylaxis. This would require a prior assessment by medical specialists from the perspective of safeguarding human health, safety, risks, benefits, etc. For this purpose, medical specialists would need to compare the goals, risks, and benefits when applying unauthorized medicinal products for treatment versus their potential application for prophylaxis, assessing their similarities and differences.

Regarding the medicinal product TPOXX, which is authorized by the FDA but lacks authorization from the European Medicines Agency, there exists a regulatory issue with its application. Despite its therapeutic purpose, it couldn't be applied based on Regulation No. 10/2011 because another approved medicinal product, specifically Tecovirimat SIGA 200 mg hard capsules, exists within the European Union territory. Additionally, the Regulation explicitly requires treatment to be conducted in hospital conditions, excluding the possibility of the medicinal product being used in outpatient settings. In a reported clinical case, Ivanov and colleagues describe two patients infected with monkeypox virus, where therapy was conservatively managed due to the lack of Tecovirimat in Bulgaria (Ivanov 2023).

Conclusion

The swift response by the Directorate-General HERA through the procurement of the Jynneos vaccine and the medicinal product TPOXX has had its impact, leading to a decline in MPOX cases in the European region. This success owes itself to the collaborative efforts of health authorities at both European and national levels.

However, questions remain regarding the use of public funds on purchasing medicinal products not authorized within the European Union but authorized for use in the United States. The application of these two products in EU member states was based on approval from the respective national competent authority for each EU member state, and recommendations from the European Medicines Agency (EMA). Furthermore, the EMA's Emergency Task Force (ETF) provided recommendations for temporary measures that national authorities could consider, given the limited supplies of Tecovirimat SIGA and Imvanex in the EU during the 2022 MPOX outbreak (EMA 2022c).

There's an inconsistency in the application of unauthorized medicinal products in countries like Bulgaria, where, according to national legislation, applying unauthorized medicinal products for prophylactic purposes (such as Jynneos) is not possible, or when there's an already approved alternative in the EU (like Tecovirimat). This discrepancy might be linked to the transposition of

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. The interpretation of this directive implies that when applying an unauthorized medicinal product, there should be no distinction between its use for prophylaxis or treatment, nor should it matter if there is another authorized medicinal product in the EU with the same therapeutic indications.

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