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Narrative review

Lessons from the European mpox outbreak: strengthening cohort research for future pandemic preparedness

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ABSTRACT

Background: Well-designed cohort studies are crucial for pandemic preparedness, informing evidence-based infection prevention and treatment strategies.
Objectives: Following the 2022 mpox outbreak in Europe, this scoping review critically evaluates the design, implementation, and characteristics of cohort studies focusing on mpox. The aim is to inform recommendations for the Cohort Coordination Board and the COordination MEchanism for Cohorts and Trials (CoMeCT) to enhance cohort study research and improve preparedness.
Sources: A comprehensive literature search was conducted in PubMed, Scopus, ClinicalTrials.gov, the European Union Clinical Trials Register, and the European Clinical Research Infrastructure Network (ECRIN) metadata repository up to December 2024.
Content: Forty-nine cohorts were identified, encompassing 10 728 individuals with primary or breakthrough mpox and 34 010 individuals without mpox (vaccinated and unvaccinated). The majority of

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Mapping
Mpox
Pandemic preparedness

cohorts collected data prospectively (30, 63%) and were multicentre (25, 52%). The primary aims were the natural history of mpox (31, 65%); effectiveness of vaccination (15, 31%); and treatment (2, 4%). The most frequent target population was individuals at increased risk of sexually transmitted infection (18, 38%). Follow-up of participants varied widely among cohorts. Significant data heterogeneity, stemming from the inconsistent use of standardized data dictionaries, impeded data sharing and meta-analyses. Under-representation of vulnerable populations and limited biobanking further compounded these challenges.
Implications: This review underscores critical gaps in the research response during the mpox outbreak. Based on these findings, we propose the following recommendations: (1) establishing and maintaining "ever-warm" cohorts of high-risk individuals during inter-epidemic periods to enable rapid data collection during future outbreaks; (2) promoting data interoperability through the development and adoption of standardized data collection tools and ontologies; (3) improving the quality of study reporting through strict adherence to relevant guidelines; and (4) strengthening European and global coordination through the establishment of collaborative research networks. Sustained investment in research infrastructure is essential for a more effective, equitable, and timely public health response to future outbreaks. **Alessandro Visentin, Clin Microbiol Infect 2026;32:62**

Background

Cohort studies are crucial for pandemic preparedness, providing a robust framework for understanding disease aetiology, investigating health trajectories, measuring vaccine effectiveness and informing evidence-based infection prevention and treatment strategies [1]. However, their usefulness for outbreak response is often hampered by the time required for study establishment, the initiation of multiple smaller studies with overlapping objectives, a lack of standardized data collection, and challenges in cross-border data sharing [2,3]. To address these limitations, the European Commission established the Cohort Coordination Board (CCB) in 2022. The CCB fosters collaboration and standardization among cohort studies investigating infectious diseases with epidemic and pandemic potential, facilitating partnership, knowledge exchange, problem-solving, and the implementation of protocols for data homogeneity and standards. Initially set-up within the Horizon 2020 ORCHESTRA (cOnnecting EuRopean CoHorts to increase common and effective rEsponSe to SARS-CoV-2 pAndemic) project, the CCB is currently integrated into the Horizon Europe VERDI (SARS-coV2 variants Evaluation in pRegnancy and paeDIatrics cohorts) and CoMeCT (COordination MEchanism for Cohorts and Trials projects. A key CCB activity is mapping European cohort studies targeting infectious diseases with epidemic and pandemic potential to facilitate data sharing and research partnerships.

The surge of clade II mpox in nonendemic countries from May 2022, particularly amongst men who have sex with men (MSM), led to its subsequent designation as a Public Health Emergency of International Concern (PHEIC) on July 23, 2022 [4], highlighting the imperative for collaborative scientific investigation [5]. Today, transmission continues, particularly in certain European subregions and among high-risk populations [6]. Herein, we critically examine the design and implementation of cohort studies targeting mpox across different populations and vaccinated and not vaccinated individuals in Europe, employing a scoping review methodology to elucidate the challenges and potential avenues for enhancing cohort studies research responses to emergent public health threats. This analysis yields crucial insights for bolstering preparedness through coordinated, prospective cohort research strategies and expands the recommendations matured within the WHO Unity Studies on respiratory diseases [7].

Mapping mpox cohort studies

For the purpose of the mapping activities in this article, a cohort was defined as any observational research study following a prespecified group of individuals over time, collecting data retrospectively or prospectively on their health outcomes, risk factors, and other relevant variables, and detecting mpox infected individuals. The search adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [8], was limited to Europe and covered the period from January 1, 2018, to Dec 10, 2024. The flowchart summarising the process (Fig. S1) as well as databases, search strategies and inclusion and exclusion criteria, are reported in the Supplementary material.

Extracted data included participating countries, primary study aims, population characteristics, collected variables, data standardization procedures, follow-up, biobanking, and funding sources. Principal investigators were contacted in case of missing data. The full list of extracted variables by cohort study is reported in the Supplementary material. For simplicity in mapping and reporting, the primary aim of each cohort study was categorised as mpox natural history, treatment and mpox vaccination, though a cohort study could cover multiple areas of investigation.

In line with the objectives of facilitating data sharing and fostering collaboration, each of the studies identified through the mapping activity can be accessed on the https://cohortcoordinationboard.eu portal [9]. The portal is equipped with a number of predefined filters, as well as the open-text filter supporting browsing across all the study descriptors and interactive visualisation showing the geographical distribution of the clinical studies.

Characteristics of European cohorts on mpox

A total of 49 cohort studies, encompassing 10 728 individuals with mpox primary or vaccine breakthrough infection and 34 010 without mpox (vaccinated and not vaccinated), were identified from the review of publications (40 cohort studies), research databases and repositories (four cohort studies), and consultations with CCB and CoMeCT networks (five cohort studies). One cohort study was excluded because of its premature termination due to insufficient enrolment, resulting in a final sample size of 48 cohort studies. The main objectives of cohorts are illustrated in the Supplementary material (Fig. S2). The variables reported across the cohorts and geographical characteristics are presented in Fig. 1, while study timelines are reported in Fig. 2. References for all cohort studies are reported in the Table S1.

The majority of cohorts collected data prospectively (30, 63%) and were multicentre (25, 52%). The primary aims were as follows: natural history of mpox (31, 65%); effectiveness of mpox vaccination (15, 31%); and mpox treatment (2, 4%). Forty-five cohort studies included adult participants, two included adults and children, and

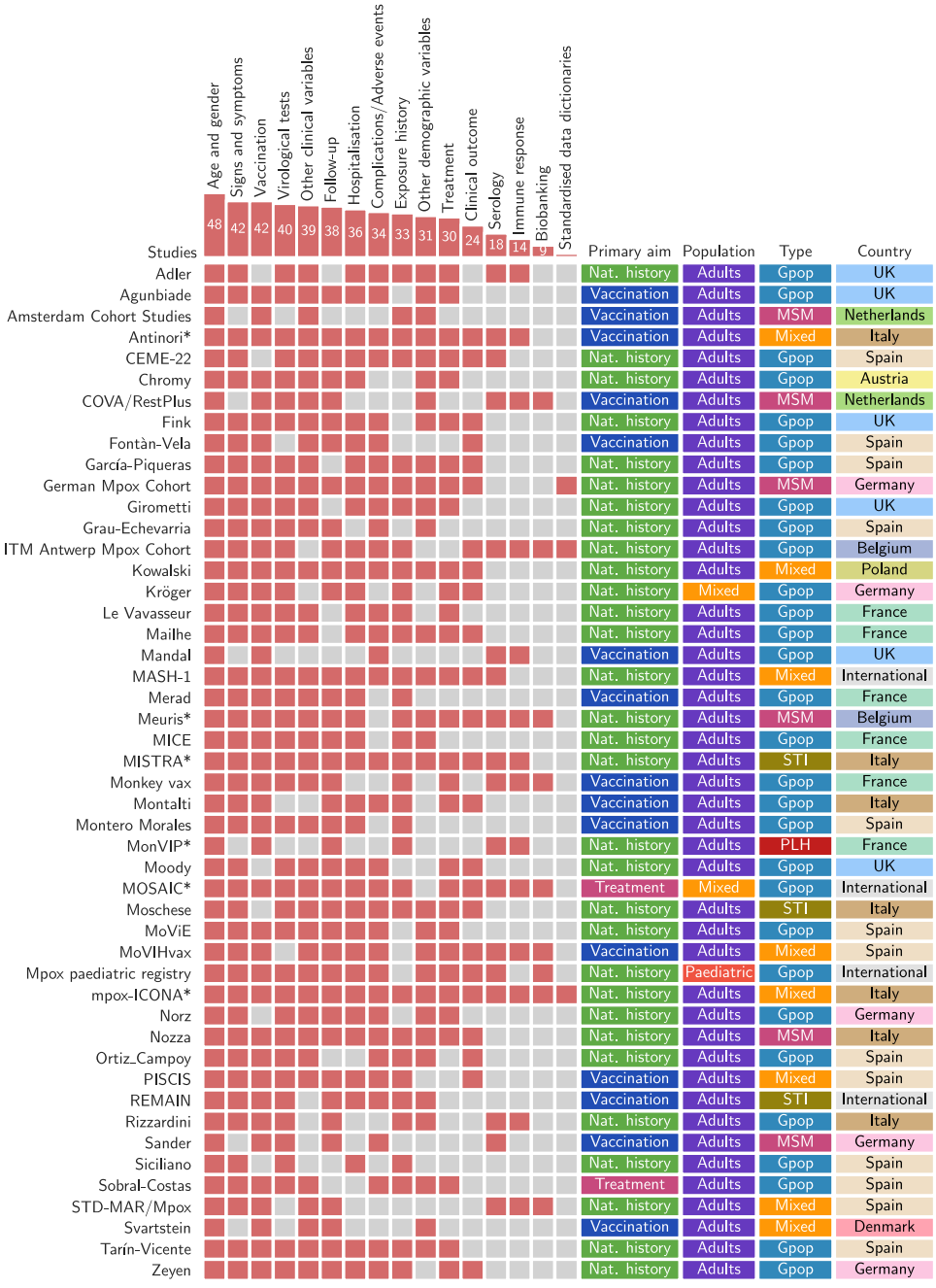

Fig. 1. Heatmap of the variables collected across different mpox cohort studies. The bar chart in the first row summarizes the total number of cohorts that collected each variable. The four columns on the right side report the primary aim, the population age, the population type and the country of each cohort, respectively. Gpop, general population; Mixed (population age), children and adults; Mixed (population type), any combination of all other populations, except Gpop; MSM, men who have sex with men; Nat. History, natural history; PLH, people living with HIV; STI, sexually transmitted infection clinic attenders. An asterisk * denotes cohort studies included, in whole or in part, in MOSAIC cohort as subcohorts.

one focused only on children. Eighteen cohorts (38%) targeted populations with increased risk to sexually transmitted infection (STI) exposure, namely STI clinic attendees (three cohort studies, 6%); people living with HIV (1, 2%); MSM (6, 13%); and a combination of these (8, 17%). Study settings were diverse, including outpatient clinics (20 cohort studies, 42%), outpatient clinics and hospital wards (16, 34%), vaccination centres (4, 8%), hospital wards (3, 6%), primary care (2, 4%), outpatient clinics applying telemedicine (1, 2%), and a combination of primary care, outpatient clinics, and hospitals (2, 4%).

The most frequently reported variables were age and gender (all cohort studies), signs and symptoms of mpox and vaccination status (42 cohort studies, 88%). Biobanking available for future analyses was explicitly mentioned in nine cohort studies (19%). Standardized data dictionaries were reported to be implemented in three cohort studies (6%).

Enrolling centres were predominantly located in Western and Central Europe (47 cohort studies, 98%). Three cohorts (6%), nominally ICONA, PISCIS, and MISTRA, were already operational before the mpox outbreak in Europe and were repurposed, whereas 40 (83%) were implemented in 2022. Study enrolment varied from 1 month to 37 months, with nine cohort studies (19%) ongoing at the time of search. Follow-up of participants after mpox diagnosis varied widely and was mostly limited to symptoms resolution; 11 cohort studies (23%) reported assessments beyond 3 months.

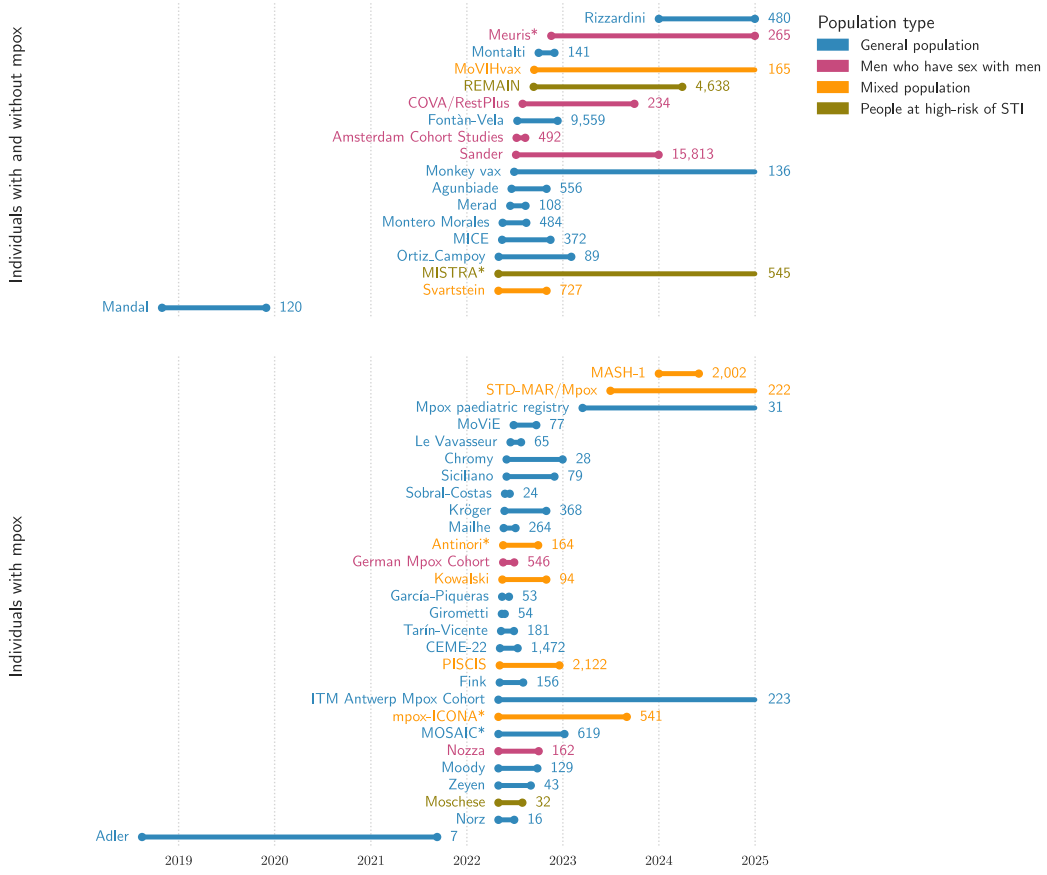

Fig. 2. Study timeline, population type and sample size for each cohort. Upper section of the Figure indicates studies that include individuals with and without mpox while lower section of the Figure indicates studies that include only individuals with mpox. If the start of enrolment was not specified, the year of study reporting was used as a proxy. End dates represent the end of enrolment where available, otherwise date of publication was reported. An asterisk * denotes cohort studies included, in whole or in part, in MOSAIC cohort as subcohorts. STI, sexually transmitted infection.

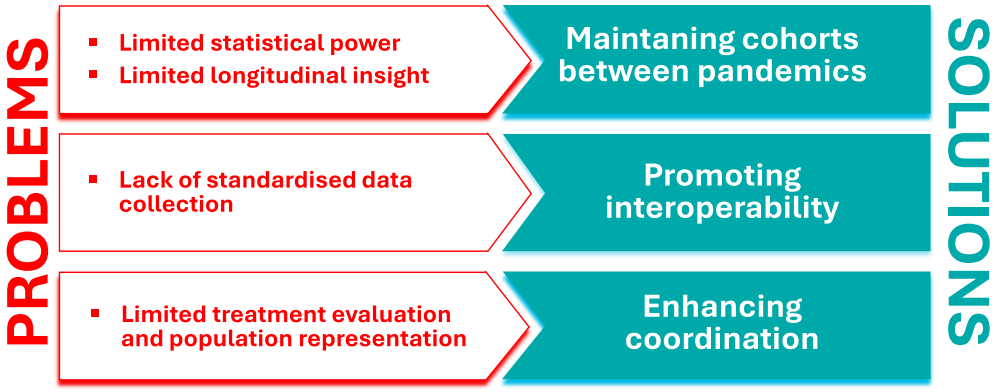

Fig. 3. Identified problems and possible solutions to improve the design and implementation of European cohort studies focusing on mpox.

Funding sources were reported for 16 cohort studies, with seven cohort studies having more than one funding source (Table S2).

Addressing critical gaps in preparedness cohort research: lessons from the mpox outbreak

Our findings show that the 2022 mpox outbreak and the PHEIC designation triggered a substantial increase in European cohort studies investigating mpox across different populations, demonstrating research community responsiveness. However, findings also highlight the persisting fragmentation of the European research landscape, ultimately missing opportunities for collaboration and hampering the generation of robust evidence. Identified challenges and potential solutions are summarized in three main areas in Fig. 3, and further outlined below.

Shortcomings in Mpox cohort studies

Limited statistical power and longitudinal insights

The first main challenge of studies identified was the modest number of mpox cases in individual cohorts (which could also be

associated to the rapid decline in case numbers) that reduced the statistical power to detect subtle effects or conduct in-depth subgroup analyses. Furthermore, longitudinal follow-up was severely limited, with most studies concluding within three months. This constraint precluded robust assessment of long-term mpox sequelae and vaccine effectiveness, hindering the development of evidence-based public health interventions and targeted vaccination strategies.

The second main challenge was a lack of standardized data collection, including inconsistent use of common data elements and electronic case report forms (eCRFs). This absence of standardization impeded data harmonization and pooling across studies, further limiting the ability to generate comprehensive insights from the collective research effort and underscoring the urgent need for a coordinated, standardized approach to data collection *from the outset* of any public health emergency. This includes the prospective implementation of common data elements and eCRFs to facilitate data harmonization and pooling across studies during epidemics. Furthermore, while standardization procedures may have been utilized in some cohort studies, inconsistent reporting practices hampered a comprehensive evaluation of their adoption and impact [2,10].

Gaps in treatment evaluation and population representation

Another key gap is the limited number of cohort studies evaluating treatment effectiveness, likely reflecting the relatively low case of severe disease, difficulties in drug supplies, and lack of standardized treatment guidelines [11–14]. The substantial focus on adults, while in line with the European epidemiology, constitutes a major knowledge gap in terms of pandemic preparedness, especially towards vulnerable populations. These can be defined as individuals or groups facing a disproportionately increased risk of adverse health, social, and economic outcomes during outbreaks and who may experience significant barriers to accessing or benefiting from standard preparedness and response measures [15]. Examples of such groups, which include the elderly, children, pregnant women, individuals living in poverty, migrants, refugees, and asylum seekers, that are specific to the mpox case are summarized in Table S3. Geographical disparities could be due to chance or varying transmission dynamics, thus limiting the generalizability of findings, but also underscore the need to improve the coverage of cohorts during outbreaks (Table S4).

Recommendations for a more integrated cohort research landscape

Based on these findings, we propose the following recommendations for a more integrated and effective approach to cohort research as part of pandemic preparedness and rapid response.

Sustaining research capacity: maintaining cohorts between outbreaks

As evidenced in the scoping review, three perpetual cohorts targeting HIV individuals and those at high-risk for STI exposure were in place before the 2022 mpox outbreak. Two of them were instrumental in the rapid expansion of the international MOSAIC cohort [16], contributing to 45% of global patient enrolment and to long-term safety assessments (currently underway). Their preexisting infrastructure, including patient consent for research entering the cohort and biobanking, highlighted the critical role of sustainable cohort platforms in pandemic preparedness, especially of those based on chronic conditions or with recurrent follow-up. Previous notable examples include perpetual HIV and HBV cohorts, which not only substantially contributed to the definition and management of long-term effects of antiviral drugs [17–20] but also supported assessment of disease severity and vaccine response during the SARS-CoV-2 pandemic [21–23] and health care system disruption [24]. Integrating such cohorts into pandemic response plans could ensure rapid data and sample collection using standardized protocols.

Ideally, an ever-warm network of geographically diverse cohorts covering a range of infectious disease threats or syndromes (e.g. respiratory infections, STIs, and Arboviruses) and underserved high-risk populations (e.g. pregnant women, children, and immunocompromised individuals) could be maintained during inter-outbreak periods similarly to what was advocated by the coordinators of the Unity Studies [7], thus enhancing research efficiency. A plurality of settings, including hospitals, emergency departments, outpatient clinics and the community, would enhance inclusion, improve coverage and provide better disease estimates. This is particularly important when it comes to community cohorts, which could help improve diagnosis, testing access and reduce hospital burden, and were successfully employed to investigate respiratory viruses and SARS-CoV-2 [25,26]. Vulnerable populations would be prime candidates because they usually experience poorer health outcomes [27] and could constitute groups at higher risk for transmission. Barriers to their inclusion in cohort research would be different according to the pathogen or syndrome under investigation but should be addressed according to guidance documents [28]. Crucially, surveillance systems should be linked to cohort studies to identify potential sites for reactivation or participants for priority inclusion, thus improving the cost-effectiveness of preparedness research, informing about relevant risk factors and allowing the assessment of the public health impact of interventions [29,30].

This integrated approach, supported by robust biobanking, could leverage observational data to inform serological studies or clinical trials based on the evaluation of preliminary effects, to allow counterfactual prediction or to emulate target clinical trials when randomized data are not available [31–33]. An example is provided by Navarro et al. [34], who emulated a target trial estimating the real-world effectiveness of mpox vaccination from well-curated electronic health records with available follow-up. Cohorts could also provide trials with accelerated patient enrolment and vital post-intervention follow-up, thus assessing their long-term impact. This was the case of the ORCHESTRA cohort data on immunocompromised individuals, which ultimately supported the indication for a booster SARS-CoV-2 vaccine dose in this patient population [35]. Nevertheless, the sustainability of perpetual cohorts would require constant, complex funding mechanisms, to either support existing national cohorts or to build national research capacity. While the new European Partnership [36] is developing a plan to enhance overall European capacity, individual countries will ultimately need to assume financial responsibility for selected sites at local level. In this context, an overarching coordination strategy is crucial. It would be the sole mechanism capable of supporting standardized protocols, ensuring homogeneous data, and managing effective cohort and clinical trials. This approach would prevent overlapping resources and studies while guaranteeing equitable access and participation.

Enhancing data utility: promoting interoperability

Improved cross-study data interoperability to promote data FAIRness [37] can support future studies, including meta-analysis, trial emulation and modelling, maximizing the value of European research investments. This is true not only for clinical data but even more so for laboratory data, where centralized analyses are impractical outside of biobanking due to technical and legislative

hurdles. The resort to data harmonization is essential to ensure comparability and is especially useful for specialized, in-house analyses (e.g. interleukin production, antibody response, etc.) or in case of previously unknown threats with no marketed product. The substantial work led by the WHO and the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) during the COVID-19 pandemic, and continued to date for mpox as well as other infections, including the development of core datasets, core outcome sets and eCRFs [38–40], provides a valuable example. Another example is the eCRF developed by the CCB to assess long-term sequelae of viral infections, based on the experience of long COVID [41]. In order to increase generalizability and transferability of results, researchers should consider using existing standardized eCRFs (e.g. ISARIC-bridge, https://isaric-bridge.replit.app/) [42], standardizing their data variables according to the existing ontologies (e.g. SNOMED-CT, LOINC, NCIT, etc.) or, in case of new threats, early submit requests for new standards to relevant organizations and stakeholders. However, the selection of any particular ontology is less important than the use of existing standards, as they can be mapped to each other. The adherence to reporting guidelines should also be encouraged, especially in EU-funded projects, as it would increase data quality when planning future reuse.

Strengthening collaboration: enhancing coordination

The EU Global Health Strategy underlines the responsibility of the EU in addressing public health threats also beyond its borders [43]. This is apparent for mpox, where there are marked differences in the geographical distribution of cases and clades worldwide. A more coordinated approach at the EU level could support global cooperation by establishing shared protocols for laboratory analyses, sharing core datasets and biobanking capacity, and participating to joint funding calls.

Ongoing initiatives like Ecraid (https://www.ecraid.eu/) [44], CoMeCT (https://comectproject.org/) [45], PROACT-EU Response (https://proact-response.eu/) [46], Be Ready (https://beready4pandemics.eu/) [47], and the future European Partnership for Pandemic Preparedness [36] represent crucial steps towards strengthening our capacity to respond to future epidemics and pandemics. CoMeCT, including the CCB and the Trial Coordination Board (TCB) aims to enhance existing coordination mechanisms for cohorts and trials on infectious diseases with epidemic and pandemic potential at the EU level. Among several actions to support collaboration among European research centres, study sites identified within CoMeCT's mapping activities are displayed on a public and constantly updated metadata repository [9] and can be leveraged by other initiatives focusing on preparedness and by institutional stakeholders, thus reducing duplication of efforts and ensuring sustainability [45]. The TCB and the CCB central mission revolves around fostering partnerships between diverse research cohorts' and clinical trials teams, promoting the sharing of best practices, data standardization and harmonization, and the alignment of research targets. Most importantly, recent networks for research in this field, such as Ecraid and PROACT-EU, are working to build robust infrastructures linking perpetual cohorts, clinical trials, and laboratory networks. The final goal of all these activities, and in particular of the European Partnership for Pandemic Preparedness is to create a unique European coordination mechanism under a network of networks. The establishment, consolidation, and further development of ever-warm European networks and infrastructures for clinical research, interventional trials, and cohort studies for public health interventions and their integration with existing national and international surveillance systems is foreseen as a key pillar of the future effective European response to epidemics and pandemics.

Study limitations

The mapping activity we performed has limitations. Relying on published literature and registered protocols may have led to the exclusion of unregistered or unpublished cohort studies. However, consultation with the CCB research network may have mitigated this to some extent. Furthermore, the accuracy of the information relies on the completeness of published reports and registry entries. Potential publication bias towards positive findings may have influenced the identified cohorts. Variations in reporting standards across different data sources may have introduced inconsistencies in the extracted information. Transferability of recommendations to low-income and medium-income country is limited since evidence has been extracted from the European context. However, the underlying principles and lessons learnt could serve as a catalyst for discussion and action also in low-income and medium-income countries. By highlighting these issues, our paper encourages researchers and public health officials in these regions to proactively design their own context-specific research cohorts and collaborative frameworks, ultimately strengthening their capacity to respond to future pandemics.

Conclusion: a call for proactive investment

This analysis provides valuable insights into the current landscape of mpox cohort studies in Europe, highlighting both strengths and critical areas for improvement. Our findings are broadly applicable to other cohort studies collecting data on infectious diseases with epidemic and pandemic potential, underscoring the urgent need for a coordinated and standardized approach to data collection and the establishment of responsive, collaborative cohort networks, particularly between outbreaks.

Crucially, cohorts could serve as a vital springboard for clinical trials and have the potential to strengthen the wider European research infrastructure. A proactive investment in robust cohort networks could ensure a more rapid and effective response to future outbreaks, enabling the collection of comprehensive data that adequately represent also at-risk and underserved populations. This data will be invaluable in informing public health initiatives, guiding resource allocation, and developing targeted interventions.

Dedicated funding and initiatives should prioritize the development of standardized data collection tools, such as common eCRFs and core outcome sets, and foster collaboration through coordinated cohort networks. Ultimately, a unified and coherent research strategy, implemented proactively and alongside international partners and stakeholders, will not only enhance our understanding of emerging infections like mpox but also strengthen European readiness to emerging and re-emerging infections and improve public health outcomes for all.

CRediT authorship contribution statement

Evelina Tacconelli: Conceptualization, writing—original draft; writing—review and editing. **Alessandro Visentin:** Conceptualization, writing—original draft; writing—review and editing, Data screening and extraction. **Alessandra Nazeri:** Conceptualization, writing—original draft; writing—review and editing, Data screening and extraction. **Rosanna Louise Flett:** Conceptualization, writing—original draft; writing—review and editing. **Ruth Joanna Davis:** Conceptualization, writing—original

draft; writing—review and editing. **José Luis Peñalvo:** Writing—review and editing. **Ali Judd:** Writing—review and editing. **Carlo Giaquinto:** Writing—review and editing. **Quentin Gaday:** Writing—review and editing. **Victoria Charlotte Simensen:** Writing—review and editing. **Nina Langeland:** Writing—review and editing. **Massimo Mirandola:** Writing—review and editing. **Liem Binh Luong Nguyen:** Writing—review and editing. **Valentina Mazzotta:** Writing—review and editing. **Christophe Van Dijck:** Writing—review and editing. **Beatriz Mothe:** Writing—review and editing. **Andreas Meyerhans:** Writing—review and editing. **Christoph Boesecke:** Writing—review and editing. **Anna Gorska:** Data screening and extraction, Figure design. All authors have read and approved the final version of the manuscript.

Transparency declaration

Potential conflict of interest

A.G. reported salary grants from VERDI and CoMeCT (101045989 and 101136531), A.J. reported EU funding to her institution (101045989 and 101136531), A.M. reported institutional grants funding his research activities (PID2022-141395OB-I00 funded by MICIU/AEI/10.13039/501100011033 and by ERDF/EU and SGR00176 grant from the Departament de Recerca i Universitats de la Generalitat de Catalunya), A.N. reported salary grant from VERDI (101045989), C.B. reported grants from DZIF, NEAT-ID, DFG as well as consulting fees, honoraria and support for attending meetings and for travel from Abbvie, Gilead, JnJ, MSD, and ViiV and a leadership role in EACS, C.V.D. reported salary grant nr. 12B1M24N from Research Fund - Flanders (FWO), Q.G. reported grants and contracts from Institut Pasteur (ANR-18-CE11-0017 and ANR-21-CE11-0003) as well as CoMeCT (101136531). All other authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2025.08.019.

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