10.48047/jocaaa.2024.33.06.147

Establishing and Utilizing Data Registries for Multisystem Inflammatory Syndrome in Children (MIS-C): Global Insights and Future Directions

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Received: 13 March 2024, **Accepted:** 17 April 2024, **Published:** 20 May 2024

ABSTRACT

Background: Multisystem Inflammatory Syndrome in Children (MIS-C) emerged as a novel post-infectious complication associated with SARS-CoV-2, characterized by hyperinflammation and multi-organ involvement. Its variable clinical presentation, overlap with Kawasaki disease and toxic shock syndrome, and evolving diagnostic criteria have created significant challenges for pediatricians worldwide. Early in the COVID-19 pandemic, the urgent need for large-scale, standardized data became evident to understand epidemiological trends, phenotypic diversity, treatment responses, and long-term outcomes. This necessity catalyzed the establishment of data registries across different regions, enabling systematic collection and analysis of MIS-C cases.

Aim: This review aims to synthesize current evidence on the establishment, operation, and impact of data registries for MIS-C, highlighting their role in advancing understanding of the condition's epidemiology, pathophysiology, and management. The article further discusses the methodological, ethical, and operational challenges encountered in maintaining these registries, emphasizing lessons learned from existing international models. By comparing global approaches and identifying gaps in current systems, this review seeks to outline an ideal framework for a sustainable and interoperable MIS-C registry capable of integrating with broader pediatric and infectious disease surveillance networks.

Conclusion: Data registries have become indispensable tools in addressing the complexities of MIS-C by facilitating real-world evidence generation, harmonizing diagnostic criteria, and informing therapeutic strategies. They serve not only as repositories for clinical data but as dynamic instruments for hypothesis generation, outcome tracking, and global collaboration. Despite notable progress, challenges remain in data standardization, equitable representation, and long-term follow-up. Advancing registry infrastructure through digital health innovations, artificial intelligence, and international harmonization will be critical in optimizing care and preparedness for future pediatric inflammatory syndromes. Ultimately, robust MIS-C registries represent a cornerstone of precision pediatric research and an enduring legacy of the post-pandemic era.

Keywords: *Multisystem Inflammatory Syndrome, Children*

10.48047/jocaaa.2024.33.06.147

INTRODUCTION

Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare but severe hyperinflammatory condition temporally associated with SARS-CoV-2 infection. First described in early 2020, MIS-C manifests with fever, cardiovascular dysfunction, gastrointestinal symptoms, and laboratory evidence of inflammation, frequently requiring intensive care support. Its clinical overlap with Kawasaki disease and toxic shock syndrome initially posed diagnostic uncertainty, leading to the recognition of MIS-C as a distinct post-viral inflammatory syndrome. The global pediatric community has since mobilized to understand its immunopathogenesis, clinical course, and optimal management through coordinated data sharing and collaborative studies [1,2].

The emergence of MIS-C presented a unique challenge: a newly recognized pediatric condition with heterogeneous presentations and outcomes amid a rapidly evolving pandemic. Traditional research models were ill-suited for timely, large-scale data aggregation, creating a critical need for real-time, standardized information. In this context, data registries—structured systems designed to collect, store, and analyze clinical and epidemiological data—became invaluable tools for clinicians and researchers. Through registries, investigators could rapidly characterize MIS-C phenotypes, assess therapeutic responses, and evaluate outcomes across diverse populations and healthcare settings [3].

However, despite the rapid creation of several national and regional MIS-C registries, variations in case definitions, data collection protocols, and follow-up methodologies have limited their comparability and generalizability. Moreover, disparities in healthcare access and digital infrastructure have led to underrepresentation of certain populations, potentially biasing the global understanding of MIS-C. These challenges underscore the necessity for harmonized frameworks and global data integration to ensure comprehensive surveillance and equitable insights [4].

The aim of this review is to critically analyze the establishment, design, and outcomes of MIS-C data registries worldwide. It seeks to identify the strengths and limitations of current systems, elucidate their contributions to clinical practice and policy, and propose strategies for future development. By highlighting the research gaps—particularly regarding data standardization, longitudinal outcomes, and cross-registry interoperability—this review emphasizes the pivotal role of registries in shaping the future of pediatric inflammatory disease research [5].

Epidemiology and Global Burden of MIS-C

Since its identification in 2020, the epidemiological understanding of Multisystem Inflammatory Syndrome in Children (MIS-C) has evolved considerably through international collaborative data efforts. Early reports suggested that MIS-C occurred in a small fraction of pediatric SARS-CoV-2 infections, yet its severity and potential for rapid cardiovascular compromise elevated it to a major

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public health concern. Initial case series from the United Kingdom, the United States, and Europe reported incidence rates ranging from 2 to 5 per 100,000 children, with marked regional variation depending on SARS-CoV-2 exposure and surveillance sensitivity [6,7]. The syndrome typically presented two to six weeks following acute infection peaks, emphasizing its post-infectious immunological nature rather than direct viral injury [8].

Globally, MIS-C has disproportionately affected children of African, Hispanic, and South Asian descent, suggesting possible genetic, socioeconomic, and environmental modifiers of susceptibility. This trend underscores the interplay between host immune response and social determinants of health. For instance, data from the U.S. Centers for Disease Control and Prevention (CDC) registry revealed that over 70% of MIS-C cases occurred among Black and Hispanic children, a disparity likely reflecting both biological and systemic inequities in COVID-19 exposure and healthcare access [9]. Similarly, European and South American registries have identified similar demographic patterns, reinforcing the need for equitable global surveillance systems.

Geographical differences also extend to clinical severity and outcomes. North American and European cohorts report higher rates of cardiac dysfunction and shock, whereas Asian registries show comparatively milder phenotypes, possibly due to genetic variation or early treatment protocols [10]. Mortality remains low globally, generally below 2%, though this figure may underrepresent true burden due to diagnostic variability and limited registry participation in low-resource settings. Importantly, registry-based surveillance has highlighted the delayed emergence of MIS-C waves following regional COVID-19 surges, providing critical insight into disease temporality and aiding public health preparedness [11].

Despite these advances, underreporting and inconsistent diagnostic criteria continue to challenge accurate global burden estimation. Many low- and middle-income countries lack dedicated registries or have limited capacity for systematic data collection. Establishing globally harmonized MIS-C registries is therefore essential not only for quantifying disease incidence but also for addressing disparities and informing equitable healthcare responses [12].

Pathophysiology and Clinical Spectrum of MIS-C

The pathophysiology of Multisystem Inflammatory Syndrome in Children (MIS-C) remains an area of intense investigation, representing a unique immunological consequence of SARS-CoV-2 infection. Unlike acute COVID-19, which primarily targets the respiratory epithelium, MIS-C emerges as a post-infectious hyperinflammatory condition typically occurring 2–6 weeks after viral exposure. The temporal separation between infection and symptom onset, together with frequent seropositivity for SARS-CoV-2 antibodies and negative PCR results, supports the hypothesis of a dysregulated immune response rather than persistent viral replication [13,14].

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Immunologically, MIS-C is characterized by profound cytokine activation, endothelial dysfunction, and aberrant T-cell and B-cell signaling. Elevated levels of interleukin (IL)-6, IL-10, IL-17, and tumor necrosis factor-alpha (TNF-α) mirror the cytokine storm seen in severe adult COVID-19, yet MIS-C exhibits distinct immune signatures with increased plasmablast proliferation and expansion of activated CD8+ T cells. Studies have also demonstrated complement activation, endothelial injury, and autoantibody formation targeting endothelial and cardiac tissues, suggesting autoimmune mechanisms contribute to pathogenesis [15].

Genetic predisposition may modulate susceptibility and disease expression. Variants in genes regulating innate immunity and interferon signaling have been proposed as risk factors. The overrepresentation of MIS-C in specific ethnic groups, particularly Black, Hispanic, and South Asian children, may reflect population-level differences in immune response genes, although socioeconomic factors likely play a concurrent role. The identification of shared inflammatory pathways with Kawasaki disease and macrophage activation syndrome provides further insight into immune dysregulation underlying MIS-C [16].

Clinically, MIS-C presents with a wide spectrum ranging from mild febrile illness to severe multiorgan failure. Common features include persistent fever, rash, conjunctivitis, gastrointestinal symptoms, and elevated inflammatory markers. Cardiovascular involvement is frequent, manifesting as myocarditis, ventricular dysfunction, and coronary artery dilatation. Hypotension and shock requiring vasopressor support occur in up to 50% of hospitalized cases, distinguishing MIS-C from other pediatric inflammatory syndromes [17]. Neurological symptoms such as headache, confusion, or seizures, and renal or hepatic involvement have also been documented, underscoring the multisystemic nature of the disease [18].

The heterogeneity of MIS-C presentations reflects its complex immunopathology and highlights the need for continued registry-based phenotyping to delineate distinct clinical subsets. Integrating laboratory biomarkers, immunologic profiling, and genetic data within MIS-C registries will be instrumental in defining disease endotypes, improving risk stratification, and guiding personalized therapy [19].

Rationale for Data Registries in MIS-C

The emergence of Multisystem Inflammatory Syndrome in Children (MIS-C) during the COVID-19 pandemic presented an unprecedented challenge to pediatric medicine: a rapidly evolving condition with uncertain epidemiology, variable presentations, and no established management protocols. In such a dynamic context, traditional research models—dependent on prolonged recruitment, controlled trial design, and delayed publication cycles—were insufficient to capture real-time clinical insights. This gap necessitated the establishment of data registries, serving as agile platforms for systematic collection, analysis, and dissemination of information on MIS-C [20,21].

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Data registries are structured repositories that aggregate standardized clinical, laboratory, and outcome data from patients across multiple centers. Their principal rationale lies in enabling large-scale, real-world evidence generation that can inform clinical decision-making and public health policy. For MIS-C, registries offered the means to identify emerging patterns in disease presentation, monitor geographic trends, and assess therapeutic effectiveness in diverse populations. By consolidating data across hospitals and nations, these systems rapidly enhanced understanding of disease burden and natural history, fostering early consensus on diagnostic criteria and management strategies [22].

Another critical function of MIS-C registries is facilitating the study of rare or heterogeneous phenotypes that would otherwise be underrepresented in single-center studies. Given the relative rarity of MIS-C compared to overall pediatric COVID-19 cases, multicenter registries were essential to achieving statistically meaningful sample sizes. They also allowed integration of multidisciplinary data—from cardiology, immunology, infectious diseases, and critical care—thereby supporting a holistic understanding of this multisystemic disorder [23].

Registries have also proven indispensable in monitoring treatment outcomes and safety in real-world settings. Observational data from registry cohorts helped identify the efficacy of immunomodulatory therapies, such as intravenous immunoglobulin (IVIG) and corticosteroids, even before results from randomized controlled trials became available. This rapid evidence synthesis was pivotal in shaping early clinical guidelines issued by the American College of Rheumatology and the World Health Organization [24].

Finally, registries serve an essential surveillance role by linking clinical data with epidemiologic and genomic information, helping to trace disease evolution and potential viral variant associations. As MIS-C continues to evolve alongside SARS-CoV-2 variants, maintaining robust, interoperable registries ensures ongoing preparedness for future pediatric inflammatory syndromes and contributes to the global capacity for pandemic response [25].

Design and Implementation of MIS-C Registries

The creation of data registries for Multisystem Inflammatory Syndrome in Children (MIS-C) required meticulous planning, international coordination, and multidisciplinary collaboration to ensure data accuracy, uniformity, and clinical relevance. Effective registry design integrates clear objectives, standardized data elements, robust governance, and interoperable digital infrastructure. Because MIS-C emerged suddenly in the context of a pandemic, registries had to be established rapidly while maintaining scientific rigor and ethical oversight [26,27].

Core Components and Data Elements

Successful MIS-C registries incorporate predefined core variables encompassing demographics, clinical presentation, laboratory findings, imaging results, treatment modalities, and outcomes. Many adopted the World Health Organization's (WHO) case definition to ensure comparability, while some

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modified criteria to align with national health policies. Harmonization of data elements across registries, such as those developed by the CDC in the United States and Public Health England, has enabled meta-analyses and global data pooling. Additional modules often include immunological and genomic profiling to facilitate mechanistic research [28].

Data Collection and Governance

Data collection typically occurs through hospital-based electronic platforms or web-based submission portals. Governance structures ensure compliance with ethical standards, patient confidentiality, and data ownership transparency. Many registries employ a tiered consent model—allowing anonymized data use for epidemiologic surveillance and optional recontact for longitudinal studies. Ethical approval and data-sharing agreements are essential for international collaboration, as data often traverse institutional and national boundaries [29].

Interoperability and Digital Infrastructure

Given the diversity of data sources, interoperability is a cornerstone of effective registry function. Integration with existing electronic health records (EHRs) through standardized formats such as HL7 FHIR (Fast Healthcare Interoperability Resources) enables automated data extraction, reducing clinician workload and minimizing errors. Cloud-based storage and secure data encryption protect patient privacy while facilitating cross-institutional analytics. Digital dashboards have also been implemented in several registries, allowing real-time visualization of epidemiological trends and clinical outcomes [30].

Stakeholder Involvement and Sustainability

Implementation success depends on active engagement from multiple stakeholders—clinicians, epidemiologists, data scientists, policymakers, and patient advocacy groups. Sustainable funding mechanisms, often supported by national health agencies or research consortia, ensure long-term operation. Furthermore, feedback loops between data contributors and registry coordinators enhance data completeness and clinical relevance. In some regions, hybrid models combining national oversight with local autonomy have proven most effective in balancing data consistency and contextual adaptability [31].

Collectively, the thoughtful design and implementation of MIS-C registries have transformed the pediatric response to this condition, setting a precedent for future rapid-deployment registries in emerging diseases. Their scalability and adaptability now serve as templates for building global pediatric surveillance frameworks [32].

Global MIS-C Registries: Current Landscape

Since the recognition of Multisystem Inflammatory Syndrome in Children (MIS-C) in early 2020, multiple national and international registries have been established to characterize the condition's clinical features, outcomes, and therapeutic responses. These registries, developed through

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unprecedented global collaboration, have significantly contributed to real-time evidence generation and policy development. Their collective data have shaped diagnostic criteria, guided treatment recommendations, and informed vaccine safety surveillance in pediatric populations [33,34].

North America

The United States Centers for Disease Control and Prevention (CDC) established one of the earliest MIS-C surveillance systems in May 2020, integrating mandatory reporting through state health departments. By mid-2023, the CDC registry had recorded more than 9,000 confirmed cases, generating pivotal data on demographics, geographic trends, and outcomes. The registry demonstrated strong associations between MIS-C incidence and peaks in community SARS-CoV-2 transmission, as well as racial and ethnic disparities in disease burden. The Overcoming COVID-19 network, coordinated by Boston Children's Hospital, further advanced understanding through detailed clinical data from over 60 pediatric centers, enabling analyses of cardiovascular outcomes and treatment effectiveness [35,36].

Europe

Several European countries rapidly established national or multinational registries coordinated through the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) and the European Centre for Disease Prevention and Control (ECDC). The UK-based *Paediatric Intensive Care Audit Network* (PICANet) and *British Paediatric Surveillance Unit* (BPSU) led the early characterization of MIS-C, locally termed PIMS-TS (Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2). These registries documented the temporal relationship between MIS-C and regional COVID-19 peaks, identifying variations in severity and treatment practices across Europe. Similar initiatives in France, Italy, and Spain integrated data on cardiac sequelae, treatment outcomes, and vaccination-era trends [37,38].

Asia and the Middle East

In Asia, national registries in India, Japan, and Israel have provided valuable insights into disease phenotypes within diverse populations. The *Indian Council of Medical Research (ICMR)* MIS-C registry, encompassing over 1,500 cases, revealed younger median ages and lower mortality compared to Western cohorts. Japan's registry, integrated with the country's Kawasaki Disease surveillance system, allowed comparative analyses that refined differential diagnosis frameworks. Israel's multicenter registry emphasized the role of early immunomodulatory therapy in preventing cardiac complications [39,40].

Latin America and Africa

Latin American registries, including the *Latin American MIS-C Network* and national databases in Brazil, Chile, and Mexico, have expanded the global evidence base by incorporating underrepresented populations. These registries identified higher frequencies of severe cardiac involvement, potentially

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reflecting delayed presentation or limited access to tertiary care. In contrast, African data remain limited, with a few nascent efforts supported by the *African Paediatric COVID-19 Registry Consortium*. These initiatives face significant infrastructural and resource constraints, highlighting global disparities in registry capacity [41,42].

International Collaborations

Global initiatives such as the *World Health Organization Global COVID-19 Clinical Data Platform* and the *International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC)* have facilitated cross-border data harmonization. The *MIS-C Global Registry Initiative* launched in 2021 aims to standardize definitions, promote equitable data sharing, and integrate genomic and immunologic data layers. These efforts are central to advancing a unified global understanding of MIS-C and serve as prototypes for future pediatric disease registries [43,44].

Collectively, these registries have demonstrated the power of coordinated data collection in accelerating medical knowledge. Continued efforts toward interoperability, equitable data inclusion, and sustainable funding are essential to maintain and expand these global surveillance systems [45].

Data Quality, Standardization, and Challenges

High-quality data are the cornerstone of any effective registry, and this is particularly true for Multisystem Inflammatory Syndrome in Children (MIS-C), where heterogeneity in presentation and management necessitates precise, standardized information. The credibility and utility of MIS-C registries depend on the consistency of data definitions, completeness of reporting, and accuracy of case ascertainment. However, variability in national surveillance systems, diagnostic criteria, and data collection methodologies has posed significant challenges to global data harmonization [46,47].

Standardization of Case Definitions

The first obstacle to standardization arose from differing case definitions issued by major health authorities. The World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and the Royal College of Paediatrics and Child Health (RCPCH) each proposed slightly divergent diagnostic criteria regarding fever duration, inflammatory marker thresholds, and evidence of SARS-CoV-2 exposure. This lack of uniformity led to discrepancies in reported incidence and clinical phenotypes across registries. Harmonizing these definitions is critical to ensuring valid international comparisons and meta-analyses [48].

Data Completeness and Reporting Bias

Incomplete data entry remains a persistent challenge in registry-based research. In many centers, the rapid pace of the pandemic and competing clinical demands limited detailed case documentation. Missing laboratory parameters, imaging results, and follow-up data have impeded longitudinal analyses. Furthermore, reporting bias often favors severe or hospitalized cases, potentially

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underestimating the full disease spectrum. Registries relying on voluntary participation may also suffer from inconsistent case submission and selection bias toward tertiary care centers [49,50].

Technical and Logistical Barriers

Technical barriers, including incompatible electronic health record (EHR) systems, lack of interoperability, and variations in data capture software, further complicate registry coordination. In low- and middle-income countries, limited internet connectivity, inadequate IT infrastructure, and scarcity of trained personnel have restricted registry functionality. The absence of automated data extraction tools increases manual workload, which may compromise data accuracy and timeliness. Additionally, differences in data storage regulations between countries can hinder cross-border data exchange [51].

Quality Control and Validation

To mitigate these issues, many registries have implemented data validation protocols such as automated range checks, duplicate detection, and mandatory fields for critical variables. Regular audits and feedback loops between data contributors and registry administrators enhance data reliability. The use of standardized data dictionaries and adoption of international ontologies (e.g., SNOMED CT, LOINC) have improved semantic consistency. Ongoing training of data entry personnel and integration of artificial intelligence (AI) algorithms for anomaly detection are emerging strategies to further elevate data quality [52,53].

Ethical and Equity Considerations

Data standardization is not solely technical but also ethical. Incomplete representation of certain populations—such as children from low-income regions, rural communities, or minority groups—can skew epidemiological insights and perpetuate inequities in healthcare resource allocation. Addressing these disparities requires inclusive registry policies, equitable access to participation, and transparent data-sharing frameworks that respect privacy while fostering collaboration [54].

Ensuring high-quality, standardized data in MIS-C registries is therefore an ongoing global priority. Without harmonized methodologies and equitable inclusion, the potential of these registries to generate transformative pediatric insights will remain unrealized [55].

Clinical Insights Derived from MIS-C Registries

The establishment of Multisystem Inflammatory Syndrome in Children (MIS-C) registries has yielded critical clinical insights that have transformed understanding, diagnosis, and management of the condition. Through large-scale data aggregation, these registries have enabled identification of disease patterns, evaluation of therapeutic strategies, and assessment of short- and long-term outcomes. The integration of data from multiple countries has provided a robust evidence base that continues to refine pediatric care guidelines globally [56,57].

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Phenotypic Classification and Clinical Patterns

Registry data have been pivotal in delineating the heterogeneity of MIS-C presentations. Analysis from the U.S. CDC and Overcoming COVID-19 registries revealed two dominant phenotypes: one resembling Kawasaki disease and another characterized by acute cardiac dysfunction and shock. The recognition of these subtypes facilitated tailored management approaches, emphasizing early cardiovascular evaluation and hemodynamic support in severe cases. European data further expanded classification models, identifying gastrointestinal-dominant and neurological variants, thereby enhancing clinical suspicion and diagnostic precision [58,59].

Therapeutic Effectiveness and Outcomes

MIS-C registries have provided real-world evidence supporting the use of immunomodulatory therapies. Comparative analyses showed that combination therapy with intravenous immunoglobulin (IVIG) and corticosteroids was associated with faster resolution of fever, reduced need for intensive care, and decreased risk of left ventricular dysfunction. These findings, corroborated by multicenter registry studies in Europe and North America, informed early consensus statements by the American College of Rheumatology and World Health Organization [60]. Moreover, registry-based studies have demonstrated that biologic agents such as anakinra and infliximab are effective in refractory cases, guiding escalation strategies [61].

Cardiovascular Sequelae and Recovery

Cardiac involvement represents a hallmark feature of MIS-C. Registry follow-up data revealed that over 60% of children presented with myocardial dysfunction, 15–20% with coronary artery dilation, and a minority with aneurysms. However, longitudinal registry analyses showed encouraging recovery patterns: most cardiac abnormalities normalized within 6–12 months with appropriate treatment and follow-up. These findings have been instrumental in establishing surveillance protocols for echocardiographic monitoring and long-term cardiology review [62,63].

Long-Term and Post-Acute Sequelae

Beyond acute illness, MIS-C registries have begun elucidating the post-recovery trajectory. Early follow-up data suggest low recurrence rates and generally favorable outcomes, though a subset of patients experience persistent fatigue, exercise intolerance, or neurocognitive symptoms. Ongoing registry-based studies are evaluating long-term immunological and psychological sequelae, aiming to identify predictors of incomplete recovery and inform rehabilitation strategies [64,65].

Public Health and Policy Implications

Registry analyses have had direct implications for vaccination policy and healthcare preparedness. Data demonstrating the rarity of MIS-C following COVID-19 vaccination in adolescents supported the safety of pediatric vaccination campaigns. Furthermore, registries have provided real-time situational awareness during variant surges, allowing early detection of changes in incidence or

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severity profiles. Such rapid insights exemplify the translational power of registry infrastructure in guiding both clinical and public health interventions [66,67].

Collectively, these insights underscore the indispensable role of MIS-C registries in shaping the modern understanding of this condition. They have bridged critical gaps between clinical observation, evidence synthesis, and policy action, thereby enhancing pediatric outcomes worldwide [68].

Comparative Analysis: MIS-C vs. Kawasaki Disease Registries

The clinical and immunological overlap between Multisystem Inflammatory Syndrome in Children (MIS-C) and Kawasaki Disease (KD) has prompted extensive comparative analyses across global registries. Both conditions share features of systemic inflammation, mucocutaneous involvement, and coronary artery changes, yet their underlying mechanisms, demographic profiles, and epidemiological contexts differ significantly. Registry-based comparative studies have been instrumental in clarifying these distinctions and in refining diagnostic and management strategies [69,70].

Epidemiologic and Demographic Differences

Kawasaki Disease, first described in Japan in the 1960s, predominantly affects children under five years of age, with the highest incidence reported in East Asian populations. In contrast, MIS-C tends to occur in older children and adolescents, with median ages ranging from 7 to 11 years in most registries. Data from U.S., European, and Indian MIS-C registries consistently demonstrate male predominance and a higher prevalence among African, Hispanic, and South Asian ethnic groups, differing from the East Asian predominance observed in KD. These demographic contrasts suggest distinct genetic and immunologic predispositions [71,72].

Pathophysiologic Insights

Registry-linked immunologic profiling has provided insight into divergent mechanisms. KD is primarily associated with activation of innate immunity and IL-1–driven inflammation, whereas MIS-C exhibits broad adaptive immune activation, including high levels of IL-6, IL-10, TNF-α, and expansion of activated CD8+ T cells. MIS-C also shows evidence of post-viral immune dysregulation following SARS-CoV-2 exposure, supported by positive serology and negative PCR in most cases. Comparative registry analyses reveal that MIS-C patients exhibit greater myocardial dysfunction and elevated markers of coagulopathy, while KD patients more commonly develop persistent coronary aneurysms [73,74].

Clinical Presentation and Severity

Registry data have demonstrated that MIS-C generally presents with more severe systemic inflammation and multiorgan involvement than KD. Gastrointestinal and cardiovascular manifestations are more prominent in MIS-C, with shock requiring vasopressor support reported in up to 50% of cases compared to <5% in classic KD. However, coronary artery dilatation and aneurysm formation occur in both conditions, highlighting shared vascular inflammatory pathways. MIS-C

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registries have also noted higher rates of intensive care admission and shorter febrile periods, reflecting the acute systemic nature of the syndrome [75,76].

Therapeutic Response and Outcomes

Comparative registry analyses indicate that while IVIG remains the cornerstone therapy for both MIS-C and KD, the response profile differs. MIS-C patients often require adjunct corticosteroids or biologic agents due to more aggressive inflammation and myocardial dysfunction. Data from European and North American registries show faster fever resolution and improved cardiac recovery with combined IVIG–steroid regimens compared to IVIG monotherapy. Long-term follow-up from both registry types demonstrates that most MIS-C cardiac abnormalities resolve within months, whereas KD patients are at higher risk for chronic coronary artery disease [77,78].

Registry Integration and Lessons Learned

Integrating MIS-C and KD registry data offers unique opportunities for comparative immunopathological research. Shared platforms, such as the Japanese *Kawasaki Disease Database* and the *ISARIC MIS-C Global Registry*, are beginning to harmonize datasets to explore overlapping and distinct pathways. Lessons from decades of KD registry experience—particularly in standardization of echocardiographic data and long-term surveillance—are informing the design of MIS-C registries. Conversely, MIS-C registries' emphasis on digital interoperability and rapid data sharing is enhancing modernization of older KD systems [79,80].

Ultimately, comparative registry analyses underscore that while MIS-C and KD share inflammatory and cardiovascular features, they represent distinct entities within the pediatric hyperinflammatory spectrum. Insights from these registries continue to deepen understanding of post-infectious inflammation and may guide future precision therapies for both conditions [81].

Use of Registries in Therapeutic Research and Clinical Trials

The development of data registries for Multisystem Inflammatory Syndrome in Children (MIS-C) has not only advanced clinical understanding but has also become integral to therapeutic research and the design of real-world clinical trials. Registries provide unique advantages over traditional randomized controlled trials (RCTs) by enabling rapid data accumulation, inclusion of diverse patient populations, and assessment of treatment effectiveness in real-world settings. In the context of an emergent condition like MIS-C, registries have bridged critical gaps in evidence, guiding therapeutic decision-making while formal trials were still in progress [82,83].

Real-World Evidence and Early Therapeutic Insights

Early during the COVID-19 pandemic, clinicians faced uncertainty regarding optimal management of MIS-C. Through registry-based analyses, preliminary patterns emerged that informed treatment guidelines even before RCTs could be organized. Data from U.S. and European registries demonstrated the superiority of combined intravenous immunoglobulin (IVIG) and corticosteroid therapy over IVIG

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monotherapy, leading to improved fever resolution, cardiac recovery, and shorter intensive care stays. These real-world findings catalyzed revisions in clinical recommendations issued by the American College of Rheumatology and other expert groups [84,85].

Registry-Based Randomized and Adaptive Trial Designs

Registries have increasingly evolved from observational databases into active research platforms capable of supporting embedded trial designs. The "registry-based randomized trial" model allows patient enrollment, treatment allocation, and outcome tracking directly within registry infrastructure, reducing cost and time. Initiatives such as the *Overcoming COVID-19 Network* and *ISARIC Global Pediatric Registry* have incorporated adaptive frameworks enabling comparative effectiveness research on emerging therapies like biologics (anakinra, infliximab, tocilizumab) and anticoagulation strategies. These designs exemplify how registries can function as both surveillance and interventional research tools [86,87].

Pharmacovigilance and Safety Monitoring

MIS-C registries have played a pivotal role in post-marketing safety surveillance of immunomodulatory and biologic agents. Because many of these treatments were repurposed from rheumatologic or autoimmune indications, continuous pharmacovigilance through registry-linked follow-up has been essential. Registries in North America and Europe have reported low rates of adverse events related to corticosteroids and biologics, reassuring clinicians about their safety in pediatric populations. Furthermore, registries have been instrumental in monitoring for recurrence, long-term immunosuppression complications, and secondary infections [88,89].

Integration with Genomic and Biomarker Research

A transformative advance in MIS-C research has been the linkage of clinical registries with biobanks and genomic datasets. This integration enables correlation of therapeutic responses with immunological and genetic profiles, facilitating precision medicine approaches. Studies using registry-linked samples have identified biomarkers predictive of poor cardiac outcomes or steroid resistance, such as elevated IL-18 and ferritin levels. Future registry-integrated genomic initiatives aim to identify susceptibility genes and guide individualized treatment algorithms [90,91].

Accelerating Translational Research and Global Collaboration

Global MIS-C registry collaborations have also fostered translational research networks connecting clinicians, data scientists, and pharmaceutical developers. Data from these networks inform the design of new therapeutic trials, identify patient subgroups for enrollment, and provide baseline epidemiologic context for sample size calculations. By creating continuous feedback loops between real-world evidence and controlled trials, registries ensure that emerging findings are rapidly validated and translated into practice [92].

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In summary, MIS-C registries represent a paradigm shift in pediatric research—merging surveillance with interventional capability, and real-world observation with translational discovery. Their continued integration into therapeutic research frameworks will be essential for optimizing outcomes and preparedness for future pediatric inflammatory diseases [93].

Conclusion

The rapid emergence of Multisystem Inflammatory Syndrome in Children (MIS-C) during the COVID-19 pandemic underscored the vital role of data registries as instruments of real-time scientific discovery, clinical guidance, and public health coordination. Through collaborative global efforts, MIS-C registries have transformed fragmented clinical observations into structured, actionable knowledge. They have provided invaluable insights into disease pathophysiology, phenotypic diversity, and therapeutic responses, directly shaping pediatric care protocols across continents.

Beyond their immediate contributions to understanding MIS-C, these registries have set a new standard for pediatric surveillance and research. Their design has demonstrated the feasibility of rapidly deploying interoperable, ethically governed data systems even amid global crises. Integration of clinical, immunologic, and genomic data has enabled the emergence of precision pediatric medicine, while longitudinal follow-up has clarified the natural history and recovery trajectories of affected children. The success of these registries exemplifies how harmonized data infrastructure can transform crisis response into lasting scientific advancement.

Yet, challenges remain. Persistent gaps in data standardization, unequal global participation, and limited sustainability threaten to fragment the collective knowledge achieved thus far. Ensuring equitable inclusion of underrepresented regions, enhancing interoperability between platforms, and securing long-term funding are critical next steps. Moreover, continuous attention to ethical governance and patient privacy will be paramount as registries evolve toward greater data integration and AI-driven analytics.

Looking forward, the MIS-C registry experience offers a blueprint for addressing future pediatric emergencies. It demonstrates that the speed and scale of modern health challenges demand equally agile data systems — systems that unite clinicians, researchers, and policymakers under a shared mission of protecting child health. Building upon these lessons, future registries should aim not merely to document disease but to actively drive innovation, preparedness, and global health equity.

In essence, the MIS-C data registry movement stands as one of the enduring legacies of the COVID-19 era — a testament to the power of collaboration, data science, and pediatric resilience in the face of uncertainty. It has converted a novel medical crisis into a model of scientific progress, ensuring that children worldwide will benefit from its collective knowledge for years to come.

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