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The challenges and opportunities for equitable global access to medications for paediatric rheumatology in low-to middle-income countries: a review on behalf of the Paediatric Global Task Force for Musculoskeletal Health

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Abstract

Advances in medications to treat paediatric rheumatic conditions including juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus (SLE) have transformed outcomes in well-resourced settings. Access to therapeutic agents that are an accepted standard of care in many regions of the world remains unequal. Here we review access to medications through a global paediatric rheumatology lens, examining challenges from drug development to delivery. The high cost of novel medications, combined with complex research and regulatory environments, market forces, the rarity of conditions and policy gaps, drive disparities in low- and middle-income countries (LMICs) where outcomes in children with JIA and SLE are closely linked to socioeconomic status and geography. Data concerning the prevalence of rheumatic conditions in LMICs are sparse, contributing to the under-recognition of disease burden. Clinical trials are disproportionately conducted in high-income countries, limiting global representation and knowledge of safety and efficacy across diverse populations. Additionally, medicines may technically be available, but with barriers that undermine true access. Global and regional organizations, including the Paediatric Task Force for Global Musculoskeletal Health, have advanced education, advocacy, and alignment of medicines with the WHO Essential Medicines List for children (EMLc). However, implementation at the country level remains inconsistent, and essential medicines for treating rheumatic diseases are often absent from national formularies. Addressing these inequities requires coordinated strategies: expanding and harmonizing EMLs, accelerating biosimilar approval and uptake, building a workforce and research capacity in LMICs, and embedding paediatric rheumatology within broader noncommunicable disease and universal health coverage frameworks. We

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summarize some strategic directions and aspirations within these 5 described arenas, that may help to address the global inequity of drug access.

Introduction

Rapid advances in the use of medications to treat paediatric rheumatic conditions, such as juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus (SLE), have improved outcomes in many parts of the world. While suppressing inflammation via a 'treat-to-target' strategy is an effective approach, it relies heavily on early diagnosis, prompt referral to and availability of specialist teams, and access to these newly developed, targeted, biologic disease-modifying anti-rheumatic drugs (DMARDs) [1]. Technological advances in medications, complex research and regulatory environments, market forces and policy deficits have led to a marked increase in the cost of such medicines [2]. These factors contribute to inequities in global access to medications and a divergence of outcomes in juvenile arthritis, which is directly related to socioeconomic status [3]. In this paper, we aim to review access to paediatric rheumatic disease medications in LMIC within a global context, describing as follows: (1) specific considerations for medication access in LMICs; (2) pharmaceutical development of therapies and the impact for LMICs; (3) the role of international organizations and other global initiatives to improve global access; (4) illustrative case studies (5) other legal and economic barriers to access.

Specific considerations for medication access in LMIC's

Paediatric rheumatology is a relatively new subspecialty in many parts of the world. The underlying challenges to survival and good health that are prevalent in LMICs have necessitated the prioritization of life-threatening problems such as malnutrition, maternal and neonatal health, trauma, and infectious diseases. Emerging problems such as climate change and political instability leading to food insecurity, poor living conditions and political conflicts increasingly add to this burden. Prevalence data for paediatric rheumatic conditions from LMICs are limited, especially in the most populous regions of the world. A recent effort to estimate the burden of SLE and JIA suggests that a large part of the burden of these conditions is likely to be overlooked, considering the absence of a paediatric rheumatology workforce in these areas [4, 5]. While the treatment of paediatric rheumatic conditions has not been prioritized in the past, there has been greater emphasis on global health approaches to paediatric rheumatology.[6].

Access to medication for rare paediatric conditions is a major challenge in all countries [7, 8]. Even highly resourced regions of the world have limitations in access to medications due to the rarity of disease and lack of a large evidence base. Limited prescribing indications, in addition to cost, are especially evident in countries that are not well resourced. Where the cost of medical care is not supported by the government, families are often forced to incur catastrophic expenditures that devastate financial stability [9]. While medication may be legally or technically approved for use in a specific jurisdiction, access may be hindered by unaffordability, geographic and other systematic factors resulting in medication not being accessible in a meaningful way. A recent review identified multiple factors that are significant barriers to meaningful access for medications used in paediatric rheumatology, highlighting the lack of even more affordable and available medications such as methotrexate and intraarticular corticosteroids [5, 10]. Importantly, true access should thus be defined as the patient's ability to receive medication safely at the right time and place, with adequate monitoring and support.

Demonstrating this reality, a survey of medication availability in Southeast Asia revealed that most countries in the region (apart from Laos) had access to DMARDS, parenteral corticosteroids and intra-articular steroids but that access to biological therapies was highly variable. Singapore had access to all biologics but many other countries had access to few or no biologics (e.g. Indonesia, Laos, Vietnam and Nepal) [8]. An examination of the alignment of paediatric rheumatology medications represented in the National Essential Medicines Lists of African countries revealed massive disparities, with only 8.5% of countries having medication lists fully aligned with the current WHO EML for children [11]. Furthermore, published data from the pan-African PAFLAR JIA registry, described only 2.3% of the patients with access to biological therapies, yet 18.9% of the patients had systemic JIA, among other subtypes [12].

These reports echo the analysis of the availability of biological therapies on the National Essential Medicines Lists of 138 WHO member countries, where countries with higher health spending and longevity were more likely to list biological therapies [13]. Only 34% of countries listed biologics of which Rituximab was the most common, while all countries listed at least one conventional synthetic DMARD.

Pharmaceutical development of therapies and the impact on LMIC's

Pharmaceutical companies invest large sums of money in developing therapies. The development process is at least partly in pursuit of science and the advancement of human health, but ultimately, the very existence of

modern pharmaceutical companies depends on being able to turn a profit and satisfy their shareholders. In this context, markets for rare diseases are small and scattered across the world. This introduces a major barrier to market entry, as pharmaceutical companies are less likely to register their products in markets that are, by their nature, highly regulated and have little growth potential. A drug that treats a condition affecting one child in a million will not be brought to market in less resourced parts of the world, where neither the government nor the private sector can subsidize the cost for the small number of affected children. Yet, children and their families with rare diseases are increasingly being diagnosed and presented for treatment with potentially successful, yet inaccessible therapy due to institutional and regulatory factors: a cruel and tragic fate.

Clinical trials for rare diseases

Generally, a rare disease is defined as affecting < 200,000 people in the United States or having an approximate prevalence of < 1 in 1,500 people [14]. Most, if not all, paediatric rheumatic diseases meet this definition. Conducting rigorous clinical trials in such small populations is challenging for several reasons. In paediatrics, the challenges of clinical trials are even more significant, with ethical, physiological, pharmacometric and economic concerns [15]. In paediatric rheumatic disease, the dual effect of rare diseases in paediatric populations limits clinical trials and requires thoughtful ethical solutions, including active comparators over placebos, incorporating escape arms, and open-label extensions [16, 17].

Clinical trials can, however, play a pivotal role in shaping global access to therapies in paediatric rheumatology by generating critical evidence on the safety and efficacy of treatments specifically for children, and by providing access to medicines within the trial structure. Yet, financial, political, societal, and environmental factors can impact the feasibility of performing clinical trials in LMICs [18]. Research capacity constraints, a lack of research funding and a shortage of paediatric rheumatology research expertise are contributors to this gap in data and representation. To address enrolment barriers, global paediatric rheumatology research networks have been created and have revolutionized the ability to operationalise multinational research trials. The Childhood Arthritis and Rheumatology Research Alliance (CARRA), the Paediatric Rheumatology International Trials Organization (PRINTO), the Paediatric Rheumatology European Society for Trials and Research (PRESTAR) and the Paediatric Rheumatology Collaborative Study Group (PRCSG) are key examples. These groups have coordinated dozens of trials in paediatric rheumatology, extending to over 60 countries. Despite these organizations and keen paediatric rheumatologists in LMICs, infrastructure to run clinical trials is costly and requires both government and non-government funding (e.g. advocacy groups). Additionally, the limited number of paediatric rheumatologists worldwide can result in extensive travel for care, particularly in LMICs. This can make it more challenging for families to commit to the frequency of visits required for participation in research studies [5, 19].

A global understanding of paediatric rheumatic disease also requires diverse representations in clinical trials [5, 20, 21]. In addition to expanding our understanding of the safety profile, epidemiological variability is important to our understanding of the mechanisms of disease, environmental impacts and burden of disease [22]. Although more trials are now occurring in Eastern Europe and India, owing to the lack of biologic-naive patients in the West, areas such as the Middle East and North Africa are only included in a very small proportion of the global clinical trial landscape despite having large populations [23].

Improving research on LMICs is crucial to our global understanding of disease, treatment, efficacy, safety and risks of these medications in countries with decreased access to monitoring [24, 25].

Orphan designation legislation

While legislation around clinical trials and approval of drugs to market have been crucial for ensuring safety, it dramatically increases the cost associated with drug development. With increasing cost, the financial benefit to pharmaceutical companies to pursue drug development for rare diseases has been minimal. Therefore, the Orphan Drug Act was enacted in the United States in 1983 and has since been expanded to include the European Union and Japan. These designations have allowed for a surge in the development of drugs for rare diseases, with financial support including tax incentives and grants for pharmaceutical companies specific to the development of these drugs. Unfortunately, one of the incentives is a 7-year period of "orphan drug exclusivity", where competitor companies cannot market a different version of the same drug for the same indication, allowing for a wide latitude on pricing [26]. This contributes to the increased cost of these medications and decreases their accessibility to LMICs.

Role of international organizations

Global inequities in paediatric rheumatological and musculoskeletal (MSK) care have recently been the subject of research and advocacy. The emergence of regional paediatric rheumatology organizations such as the Asia Pacific League of Associations for Rheumatology Paediatrics (APLAR) Paediatric Special Interest Group and the Paediatric Society of the African League Against

Rheumatism (PAFLAR) [12, 27], as well as global advocacy and educational efforts by the Global Task Force for Paediatric Musculoskeletal Health (TF) [28], the Paediatric Rheumatology European Society (PReS) Global Health Working Party [29], Tin Soldiers Global [30] and others have developed further interest and education in the field. Multiple educational efforts (open and free to the users), such as the APLAR and PAFLAR webinars, online resources, such as Paediatric Musculoskeletal Matters (PMM) [31, 32], and PReS hybrid basic courses, have taken advantage of the global communication revolution and aims to address gaps in education and facilitate awareness [33].

To address the global disparity in access to medicines for paediatric rheumatology, international professional and patient organizations have developed several multifaceted strategies to engage the World Health Organization (WHO) and its affiliates (Fig. 1).

Raising awareness of paediatric rheumatic conditions is the cornerstone to any strategy to improve access to care. Several international and regional organizations are continuously working towards this goal. Rare Diseases International has recently celebrated the successful adoption of the Resolution for Rare at the 78th World Health Assembly.

The Global Musculoskeletal Alliance (GMUSC) focuses on musculoskeletal (MSK) health policy and has developed an evidence-based framework for MSK health care, which includes equitable access to medicines and technologies [34]. GMUSC further highlighted the absence of MSK healthcare in the UN General Assembly Zero draft proposal for 'the control of noncommunicable diseases…', and continues to work for the inclusion of MSK health in the United Nations and national healthcare policies [35, 36].

WHO Formularies and their influence on medication accessibility

The TF, an arm of the GMUSC, has concurrently made headway in updating the WHO EML and EML for children for paediatric rheumatology [6, 28]. The decision to update the WHO EML hinged on its wide reach as a globally available clinical care reference standard, utilized in many parts of the world to inform National Essential Medicines Lists (NEMLs) and healthcare planning.

The TF submitted applications for anakinra, tocilizumab, and triamcinolone hexacetonide to be added to the WHO EML for the treatment of joint diseases in children, and more broadly advocated to update the medications listed for paediatric rheumatology. The applications were based on collective international opinions expressed in surveys conducted by the TF between 2020 and 2023 and were informed by modern treatment guidelines. The surveys also flagged the availability and affordability of medicines for paediatric rheumatology as major barriers to care [10, 37].

Medicines on the WHO EML are selected with respect to public health relevance and are intended to always be available, in appropriate dosage forms, of assured quality and at prices that individuals and health systems

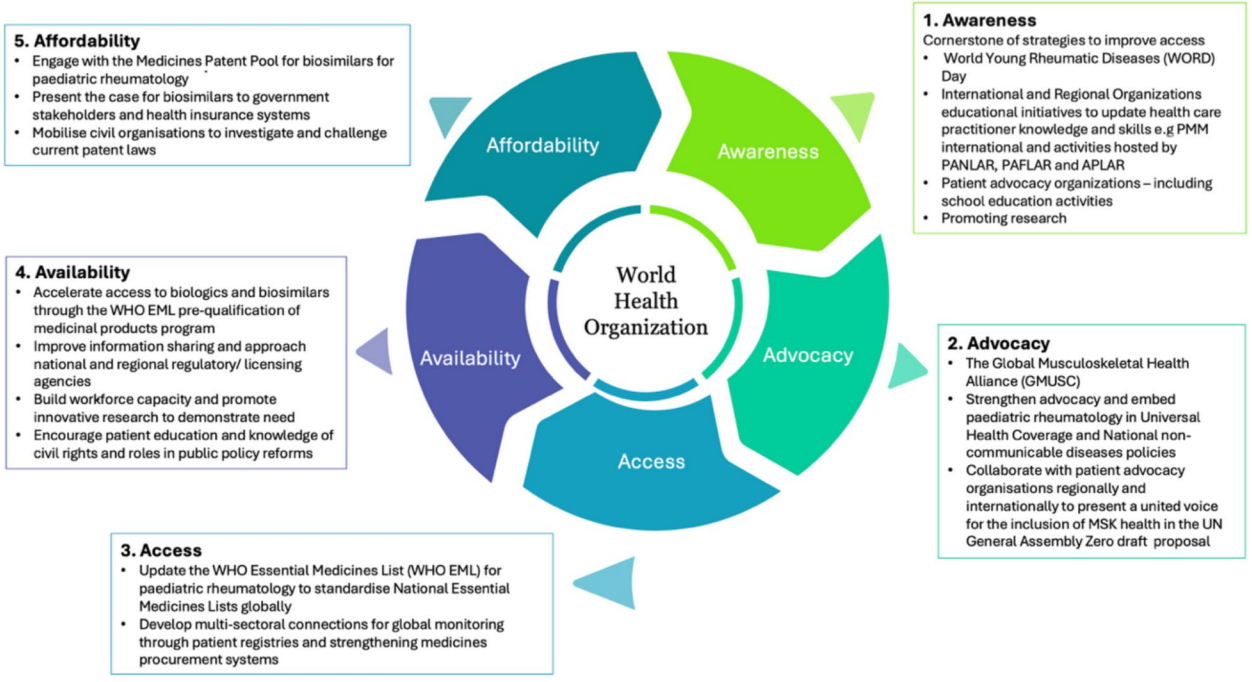

Fig. 1 Towards equitable access to medications for paediatric rheumatology

can afford. The implementation of the WHO EML is supported by the provision of technical assistance for the procurement and supply of medicines, the WHO prequalification of medicine systems to ensure quality control, fair pricing forums, and regular assessments of pricing and reimbursement systems [38]. Updating the WHO EML for paediatric rheumatology would therefore enable access to effective and affordable medicines to counter the mismatch between healthcare needs and supply, particularly in LMICs.

Since TF engagement in 2020, the WHO EML section 'Joint diseases in children' has expanded from only two medicines, methotrexate and acetylsalicylic acid, to include tumour necrosis factor inhibitors, triamcinolone hexacetonide (TH) for intra-articular injections and other disease-modifying antirheumatic drugs [39].

Work is ongoing for the addition of anakinra and tocilizumab to the WHO EML, as there are no alternative treatment options for systemic juvenile idiopathic arthritis (sJIA) with and without macrophage activation syndrome. Additionally, inequities in alignment between various national EMLs and the WHO EML still need to be addressed [11].

Case studies and comparative examples

Given the complex situation regarding access to medications to treat paediatric rheumatic and musculoskeletal diseases, it is sometimes easier to understand these challenges by examining case studies. Two examples that illustrate the challenges and inequities in medication distribution that are relatively specific to paediatric rheumatology include access to anakinra and triamcinolone hexacetonide (TH). The inconsistent availability of these two medications worldwide makes providing equitable and consistent care to patients challenging. However, the principles that drive inequity are not confined solely to these two medications. They are merely illustrations of a series of larger systemic failures regarding equitable medication distribution. We observed similar disparities in regard to the use of the COVID-19 vaccine during the SARS-CoV-2 pandemic, similar to the case of distribution of antiretroviral medications used to for HIV treatment throughout the continent of Africa [40, 41].

Triamcinolone Hexacetonide (TH)

Intra-articular corticosteroid injections are a common first-line therapy for children suffering from juvenile idiopathic arthritis (JIA). They work quickly, providing relief within days, as they are injected directly into the joint space. They have a good safety profile and are efficacious. Intra-articular corticosteroid injection can help target inflamed joints to help spare children from systemic therapy, such as DMARDs or biologic agents, if only a few joints are involved. They can also be utilized as part of a comprehensive therapy plan and help patients increase joint functionality while waiting for systemic therapies to become effective [42].

The most efficacious corticosteroid for intra-articular injection is TH It was developed in the 1950 s and quickly became the first-line therapy for intra-articular corticosteroid injections in patients with JIA [43]. Prior to 2015, TH was the preferred corticosteroid because of its longer-lasting effects than those of triamcinolone acetonide (TA) The longer duration of the effect of injection in children suffering from inflammatory arthritis with TH than with TA has been demonstrated in several studies [42].

However, despite the superior efficacy and duration of TH, it is not readily available worldwide. In North America, the manufacture of TH stopped in the 2010s. This was not due to safety or efficacy concerns, but likely due to market forces. Subsequently, it is no longer readily available in North America, although some pharmacies can acquire a similar medication through imports. This decreased availability has led to patients receiving injections with the inferior TA or requiring additional escalation of systemic therapy. One study from Israel showed that the change from TH to the more soluble TA, which was the result of global shortages of TH, has resulted in a doubling of relapse rates at 40 months [44]. TH was recently approved for the WHO EML, and there is hope that this should promote increased production and access to TH in the future [39, 45].

Anakinra

Anakinra is an interleukin 1 inhibitor that is commonly used for children with sJIA and autoinflammatory syndromes. It is particularly useful for patients with macrophage activation syndrome (MAS), which is a common complication of sJIA. When left untreated, MAS is potentially fatal, and prior to the development of anakinra, MAS was treated mainly with high doses of corticosteroids, which have significant side effects. The development of anakinra has revolutionized the care of patients with autoinflammatory syndromes. Anakinra was approved for sJIA in Europe (license extension) in 2021; up until then it was only approved for the treatment of cryopyrinopathies, deficiency of IL-a and RA only. Since anakinra has historically been an off-label treatment for the indication of s-JIA many countries across the world still do not have access to it. Changes in indication and formulation of the product mean that this medication is still under patent and biosimilar medicines have not been developed to reduce the cost of this life saving medication [46]. Most of Sub-Saharan Africa and many parts of Southeast Asia do not have access to this important and potentially life-saving therapy. Other IL-1 inhibitors, such as canakinumab, are many times more costly, and their availability is far lower, even than that of Anakinra.

Other economic and legal barriers

The costs of biologics have decreased in the last few years but remain too high for use in LMICs. Table 1 indicates drug costs for the United Kingdom in 2022. These prices are illustrative but not applicable to all countries. Annual cost estimates for doses for a child weighing 20 to 50 kg are indicated for selected biologic agents.

In 2021, the Medicine Patent Pool (MPP) expanded its mandate to encompass biotherapeutics. MPP public licensing agreements promote the development of biosimilars at reduced costs and in shorter time frames when full technology transfer occurs [49].

Although tiered pricing and patient assistance programs can play a role, biosimilar-induced competition generally helps reduce costs further [49]. Work by the Generics and Biosimilar Initiative has suggested that the difference in the acquisition price between the biosimilar and reference originator should be between 15–30%. As the market share increases, biosimilars are expected to become less expensive over time [50].

To date, there are no licensing agreements for biologics used in paediatric rheumatology available via the MPP. However, several biosimilars have come to market in recent years.

Approval and regulatory agencies

Production processes notwithstanding, improving access to and the availability of biosimilars is challenging. While organisations such as the International Coalition of Medicines Regulatory Authorities (ICMRA) aim to improve communication between medicine authorities by facilitating the wider exchange of reliable and comparable information, medicine approval laws are diverse.

In South Africa, comparability to the originator molecule is necessary for biosimilar approval, whereas full clinical trials in local populations are needed in India. Accelerated regulatory approval for biosimilars with originator products already on the WHO EML via the WHO prequalification of medicines programs could significantly shorten the time frame to approval and therefore improve access and availability in participating LMICs. An alternative pathway for regulation is via the European Medicines Agency – 'EU Medicines for all' regulates medicines for use outside the European Union in support of the WHO prequalification of medicinal products program, further enabling the availability of medicines in LMICs [46, 50].

Patent laws and their implications

Additional barriers to affordability include the World Trade Organization Trade-Related Aspects of Intellectual Property (WTO TRIPS) agreement, which describes internationally accepted patent laws. These laws are applied to biologics and may also include periods of research and development. Patents for biologics have been protected for up to 20 years. Strategies to extend market exclusivity (Table 2) by limiting biosimilar development are complex. These include patent 'thickets', the launch of 'biobetters', 'evergreening', and 'pay-for-delay' of the launch of biosimilars [51]. These strategies effectively prohibit the sharing of information for biosimilar production. TRIPS flexibilities to override patents have been invoked only in major humanitarian crises.

Global advocacy efforts to improve access to trastuzumab, the monoclonal antibody used in HER2-positive breast cancer, offer an instructive parallel for paediatric rheumatology. Early after its introduction, trastuzumab remained prohibitively expensive for most LMICs, largely due to patent protections, limited manufacturing capacity, and restricted regulatory pathways for biosimilars. Sustained advocacy by civil society groups, cancer alliances, and global health organizations highlighted the unacceptable mortality gap and pressured governments and international bodies to intervene. As a result, trastuzumab was added to the WHO Essential Medicines List in 2015, generating political momentum for national formulary inclusion and facilitating pooled procurement mechanisms. Subsequent legal challenges to restrictive patents, coupled with the WHO prequalification of biosimilar trastuzumab in 2019, enabled competition that dramatically reduced prices across multiple regions. These policy, legal, and advocacy successes demonstrate how coordinated global action combining EML inclusion, regulatory support for biosimilars, and civil pressure on pharmaceutical stakeholders, can transform access to high-cost biologics and offer a roadmap for improving medication availability in paediatric rheumatology [52].

Coordinated global efforts through international advocacy organizations are essential to improve the access, availability and affordability of the medicines needed for paediatric rheumatology. By applying civil pressure, changes in policies affecting MSK healthcare and the reconsideration of patent laws for public benefit are possible.

Bridging the gap: ethical, policy, and advocacy considerations in medication access for paediatric rheumatology patients

Access to prompt quality clinical care remains a profound challenge for children living with rheumatic and musculoskeletal diseases (RMDs), especially in LMICs. Despite therapeutic advancements, disparities in access to essential medications and care persist. This is exacerbated by systemic, ethical, and economic barriers. We explore the ethical imperatives, role of advocacy, and policy landscapes shaping the availability of paediatric rheumatology care globally, anchored by practical guidance from frameworks such as the PAFLAR and the PANLAR.

Table 1 Cost estimates of medications used in paediatric rheumatology (United Kingdom 2022)

Conventional synthetic DMARDs						
International Non-proprietary Name (INN)	**Anatomical Therapeutic Chemical Classification (ATC)**	**Year of FDA/EMA approval [1]**	**Tablet/formulation unit size**	**Drug Tariff price (£) [2]**	**Annual cost (£)—50 kg child**	**Annual cost (£) 20 kg child**
Methotrexate	L04AX03	1994 tablet 2007 oral solution 2013 SC	2.5 mg tabs 2 mg/1 mL oral solution SC (different strengths)	1.88 (28) 125 (65 mL) 12.87 (7.5 mg) up to 16.56 (30 mg)	30.08–120.32 NA 768	16.92 625 672
Leflunomide	L04AA13	2005	10 mg tablets	2.51 (30)	60.24	30.12
Sulfasalazine	A07EC01	2002 Before 1982 (oral suspension)	500 mg tablets 250 mg/5 mL	32.85 (112) 94.22 (500 mL)	788.4 NA	393.84 2543.94
Chloroquine and Hydroxychloroquine	P01BA01	2003 1994 (hydroxychloroquine)	250 mg tablets 200 mg tablets	8.59 (20) 3.21 (60)	134 19.26	NA 19.26
Ciclosporine A	L04AD01	1995 2001 oral solution	25 mg capsules 100 mg/1 mL	18.37 (30) 164.7 (50 mL)	3086.16 NA	NA 988.2
Biologic DMARDs						
Tumour necrosis Factor inhibitors						
Etanercept	L04AB01	Originator 1998 FDA/ 2000 EMA Biosimilar 2016 FDA/ 2016 EMA	Enbrel 25 mg powder and solvent Enbrel 10 mg paediatric vial Enbrel PFS/Pen 25 mg 50 mg Benepali (biosimilar) 25 mg PFS 50 mg PFS	35.7 5 (1 vials) 143 (4 vials) 357.50 (4) 715.00 (4) 357.5 (4) 656 (4)	3718.00 NA 4290 8580.00 4290 7872	NA 3432.00 NA NA NA NA
Infliximab	L04AB02	Originator 1998 FDA/ 1999 EMA Biosimilar 2016 FDA/ 2013 EMA	Remicade 100 mg Remsima 100 mg (biosimilar)	419.62 (1) 377.66 (1)	15 525.94 14 728.74	10,070.88 9063.84
Adalimumab	L04AB04	Originator 2002 FDA/ 2003 EMA Biosimilar 2016 FDA/ 2017 EMA	Humira 40 mg PFS Humira 20 mg PFS Amgevita (biosimilar) 40 mg PFS Amgevita 20 mg PFS	704.28 (2) 352.14 (2)633.6 (2) 154 (1)	9155.64 NA 8236.80 NA	NA 4225.68 NA 3693.00
Golimumab	L04AB06	2009 FDA/ 2009 EMA	100 mg PFS 50 mg PFS	1525.94 (1) 762.97 (1)	NA 9155.64	NA NA
IL-6 inhibitor						
Tocilizumab	L04AC07	Intravenous 2010 FDA/ 2009 EMA SC 2013	IV 400 mg vial SC 162 mg PFS	512.00 (1) 913.12 (4)	6 144 (JIA)—13 312 (s-JIA) 5478.72 (JIA)–10,957.44 (s-JIA)	6144 (JIA) to 12,288 (s-JIA) 4565.6 (JIA) to 5478.72 (s-JIA)
IL-1 inhibitor						
Anakinra	L04AC03	2001 FDA/ 2002 EMA	100 mg PFS	183.61 (7)	9 573.95- 38,295.80	Same
Canakinumab	L04AC08	2009 FDA/ 2009 EMA	150 mg injection	9927.8 (1)	238 267.20	Same
IL 17 A inhibitor						
Secukinumab	L04AC10	2015 FDA/ 2015 EMA 2022 EMA (paediatric indications)	150 mg PFS 75 mg PFS	1218.78 (2) 304.7 (1)	16 doses incl LD: 9 750.24	Same

Table 1 (continued)

Conventional synthetic DMARDs						
International Non-proprietary Name (INN)	**Anatomical Therapeutic Chemical Classification (ATC)**	**Year of FDA/EMA approval [(1)]**	**Tablet/formulation unit size**	**Drug Tariff price (£) [(2)]**	**Annual cost (£)—50 kg child**	**Annual cost (£) 20 kg child**
IL12/23 inhibitor						
Ustekinumab	L04AC05	2009 FDA/ 2009 EMA	45 mg	PFS or paediatric vial 2147 (1)	5 doses incl LD: 1 0735	Same
CD20 inhibitor						
Rituximab	L01FA01	Originator 1997 FDA/ 1998 EMA Biosimilar 2018 FDA/ 2017 EMA	MabThera 500 mg vial Truxima (biosimilar) 500 mg vial	873.15 (1) 785.84 (1)	6 985.2 6 286.72	Same Same
Targeted synthetic DMARDs						
Janus Kinase inhibitors						
Tofacitinib	L04AA29	2012 FDA/ 2017 EMA Oral solution. 2020 FDA/ 2021 EMA	5 mg tablets Liquid: price not yet published	690.03 (56)	8993.6	NA
Baricitinib	L04AA37	2019 FDA/ 2017 EMA	2 mg and 4 mg tablets	805.56 (28)	11 380.7	Same

Abbreviations: *PFS* Pre-filled Syringe, *IV* Intravenous, *SC* Subcutaneous, *FDA* U.S Food and Drug Administration, *EMA* European Medicines Agency. *LD* Loading dose, *NA* Not applicable due to age and or weight related dosing and formulation considerations. Compiled by Octavio (Tavi) Aragon Cuevas, Lead Rheumatology Paediatric Pharmacist, Alder Hey Children's NHS Foundation Trust [47, 48]

[(1)]EMA approval dates only given for biological medicines. DMARDs and other supportive medicines' approval dates different in the EU depending on the member country

[(2)]Cost of PEN devices is the same as PFS devices of the same strength (where available)

Table 2 Strategies to extend patents and delay biosimilar production

Terms	Accepted Meaning	Example
Patent thickets	A dense network of concurrently overlapping patents on a single product for various components, parts of the manufacturing process, different formulations or delivery methods, extend the patent protection period	Humira – 132 patents filed covering the active ingredient, formulations, manufacturing process, and methods of use. The last patents are set to expire in 2037
Biobetters	Improved versions of the existing originator, engineered with modifications to enhance outcomes. New patents can be filed due to novel molecular structure which may have increased efficacy, reduced side effects, or for improved delivery mechanisms	Trastuzumab: Subcutaneous formulation of Herceptin Infliximab: Remsima subcutaneous formulation drawing improvements on the original Remsima
Evergreening	Extending market exclusivity by obtaining additional patents on modifications or related uses of an existing originator e.g. minor adjustments to dosage, formulation or delivery	Citrate free version of Humira and Kineret
Pay-for-delay settlements	Paying companies producing biosimilars to delay their launch	Delayed Humira biosimilar launch to 2023

Ethical considerations in medication access

The principles of equity and justice in healthcare demand that all children, regardless of geography or socioeconomic status, receive prompt and appropriate treatment. However, in many parts of the world, essential medications such as methotrexate, corticosteroids, and biologic therapies remain either unaffordable or unavailable. In a recent qualitative study in Kenya, parents and guardians of children with JIA faced challenges in looking for resources and support to cope with the difficult moments of caring for their sick children [53]. This raises ethical concerns about distributive justice and the global pharmaceutical market's responsiveness to paediatric needs.

Pharmaceutical companies have a moral obligation to ensure the equitable distribution of life-saving medications. Differential pricing models expanded access programs, and technology transfer partnerships could significantly improve affordability in resource-limited settings. However, such mechanisms are underutilized in paediatric rheumatology.

Role of non-governmental organizations and advocacy groups

Nongovernmental organizations (NGOs) and patient advocacy groups have stepped in to bridge the gap where public health systems fall short. Organizations such as the PAFLAR, Hope Arthritis Foundation, the International League of Associations for Rheumatology (ILAR), and Juvenile Arthritis Research (JAR) have championed

Table 3 Proposed action items to promote equitable paediatric rheumatology care

Action	Stakeholders
Short to Medium Term Priorities	
Build clinical and research capacity for paediatric rheumatology in LMICs through improved educational and funding initiatives	• Regional paediatric rheumatology societies (PAFLAR, AFLAR, PANLAR, APLAR) • Academic institutions and medical schools • International research networks (PRINTO, PRCSG, CARRA) • Funding agencies (ILAR, Wellcome Trust, NIH Fogarty, EDCTP) • National Ministries of Health and Education • Tele-education platforms (PMM, EULAR School of Rheumatology, PReS Academy) • Professional bodies for paediatrics and rheumatology
Advocacy, policy integration and multisectoral collaboration in MSK health should be strengthened • For example, paediatric rheumatology should be embedded within national noncommunicable disease strategies and universal health coverage access strategies	• National Ministries of Health, Finance, and Social Development • United Nations agencies (WHO, UNICEF, UNDP) • Paediatric Global Task Force for Musculoskeletal Health • Global Musculoskeletal Alliance (GMUSC) • Noncommunicable disease alliances (e.g., NCD Alliance) • Patient advocacy NGOs and caregiver networks • Multisector coalitions on UHC • Regional political unions (AU, ASEAN, EU)
Medium Term Priorities	
Strengthening Multisectoral Collaboration between governments, NGOs, academics and multilateral organizations to align efforts and drive coordinated action to improve access and build supply chain resilience	• National governments (health, finance, education, trade) • WHO, UNICEF, UNDP, World Bank • International and regional paediatric rheumatology societies • Academic and clinical centres of excellence • Local and global NGOs active in medicine access and rare diseases • Pharmaceutical industry partners (originators + biosimilars) • Community and patient advocacy groups
Expanding and standardizing Essential Medicines Lists globally by pushing for the inclusion of key medications in the WHO EML and enhancing country-level alignment	• World Health Organization (WHO) Essential Medicines List Committee • National Ministries of Health & National Essential Medicines List Committees • International Paediatric Rheumatology Societies (PReS, ACR, PANLAR, APLAR, PAFLAR) • NGOs working on essential medicines access (e.g. Médecins Sans Frontières Access Campaign) • Global Musculoskeletal Alliance (GMUSC and Paediatric Global Task Force for Musculoskeletal Health) • Patient advocacy groups (Arthritis Foundations, Rare Disease organisations)
Accelerate access to affordable biologics and biosimilars by advocating to national and regional regulatory and licensing agencies	• National and regional medicines regulatory authorities • (e.g., EMA, FDA, SAHPRA) • World Health Organization Prequalification Programme • Medicines Patent Pool (MPP) • Generic and biosimilar manufacturers • Originator pharmaceutical companies • World Trade Organization TRIPS Council • Health technology assessment agencies (e.g., NICE UK, CADTH Canada)
Long Term Priorities	
Global monitoring mechanisms are implemented through registries and access score cards	• International registry networks (e.g., PAFLAR JIA Registry, PRINTO, CARRA) • WHO & regional health observatories • National Ministries of Health & national surveillance units • Academic and biostatistical institutions • Digital health innovators and data system developers
Local manufacturing can be promoted by investment in local and regional pharmaceutical manufacturing, especially in LMICs, to improve availability and reduce costs for medication for inflammatory arthritis	• Regional pharmaceutical manufacturers (India, South Africa, Brazil, Egypt) • National Ministries of Trade, Industry, and Health • Medicines Patent Pool (for licensing and technology transfer) • Multilateral financing bodies (World Bank, IFC, AfDB) • WTO TRIPS Council and IP law authorities • Regional economic communities (ECOWAS, SADC, MERCOSUR) • Public–private partnerships for biomanufacturing

awareness campaigns, supported diagnostic services, and negotiated access to medications through donations and partnerships.

These actors not only deliver care but also amplify the voices of affected families in national and global policy dialogues. Their work demonstrated that community-driven action can shift paradigms and influence systemic change, especially when rooted in culturally informed, patient-centred strategies.

Impact of health policies and insurance systems

Access to care is heavily influenced by national health policies and insurance structures. In countries with health insurance, most paediatric rheumatic conditions are not covered in the reimbursement system owing to their rarity and lack of clearly defined treatment guidelines. Countries with universal health coverage (UHCs), such as Chile and Costa Rica, have seen better outcomes in paediatric rheumatic disease management, owing to integrated services and medication coverage [54]. In contrast, fragmented or underfunded systems often lead to catastrophic out-of-pocket expenses for families, delayed diagnoses, and untreated disease progression.

Public policy reforms, including the inclusion of essential rheumatology medications in national formularies and strategic purchasing agreements, are crucial. Equally important is the training of primary care providers and paediatricians in the early identification of RMDs, a gap that can be closed through capacity-building initiatives.

National guidelines and recommendations

Guidance documents from the PAFLAR, PANLAR, Paediatric Rheumatology European Society (PReS), American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) provide actionable policy and clinical frameworks tailored for diverse contexts. For example, PAFLAR's recommendations emphasize decentralization of services, early detection through school health programs, and the establishment of centres of excellence in paediatric rheumatology. PANLAR, on the other hand, underscores integration into national noncommunicable disease (NCD) strategies and the standardization of biologic use protocols in children.

Both frameworks stress multisectoral collaboration, advocating for alignment among ministries of health, education, and finance to ensure sustainable care delivery models. These recommendations are not only relevant for Latin America and Africa but also serve as scalable models for other under-resourced settings globally.

Proposals to advance access to medication for children living with rheumatic diseases

Strategic proposals for action for short, medium and long term priorities as well as roles for relevant stakeholders are outlined in Table 3.

Conclusion

Addressing inequities in paediatric rheumatology care is a moral, clinical, and public health imperative. It demands that all stakeholders including governments, pharmaceutical companies, healthcare providers, and communities act in concert to ensure that no child suffers needlessly due to systemic neglect. Guided by ethical frameworks and inspired by grassroots advocacy, we can move toward a future where access is not a privilege but rather a right for every child with RMDs.

Abbreviations

ACR	American College of Rheumatology
AfDB	African Development Bank
AFLAR	African League of Associations for Rheumatology
APLAR	Asia Pacific League of Associations for Rheumatology
ASEAN	Association of Southeast Asian Nations
AU	African Union
CADTH	Canadian Agency for Drugs and Technologies in Health
CARRA	Childhood Arthritis and Rheumatology Research Alliance
ECOWAS	Economic Community of West African States
EDCTP	European and Developing Countries Clinical Trials Partnership
EU	European Union
EULAR	European Alliance of Associations for Rheumatology
FDA	U.S. Food and Drug Administration
GMUSC	Global Musculoskeletal Alliance
ICMRA	International Coalition of Medicines Regulatory Authorities
IFC	International Finance Corporation
ILAR	International League of Associations for Rheumatology
JAR	Juvenile Arthritis Research
MPP	Medicines Patent Pool
MERCOSUR	Southern Common Market (Mercado Común del Sur)
NICE	National Institute for Health and Care Excellence (UK)
NIH	U.S. National Institutes of Health (NIH Fogarty = NIH Fogarty International Center)
PAFLAR	Paediatric Society of the African League Against Rheumatism
PANLAR	Pan American League of Associations for Rheumatology
PMM	Paediatric Musculoskeletal Matters
PReS	Paediatric Rheumatology European Society
PRCSG	Paediatric Rheumatology Collaborative Study Group
PRINTO	Paediatric Rheumatology International Trials Organization
SADC	Southern African Development Community
SAHPRA	South African Health Products Regulatory Authority
TF	(Global) Task Force for Paediatric Musculoskeletal Health (Paediatric Global MSK Task Force)
UN	United Nations
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
WHO	World Health Organization
WTO	World Trade Organization

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Authors' contributions

C.S and A.M conceptualised the manuscript and assembled writing team. C.S,A.M, W.S,M.D,E.H and H.F completed the main manuscript first draft, C.S,A .M,W.S,M.D,E.H,H.F,A.F,C.N,F.F,J.M,D.H, O.A.C critically reviewed and revised the manuscript. W.S prepared Fig. 1 O.A.C prepared Table 1.

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