Accelerating access to paediatric medicines: lessons learned from the Global Accelerator for Paediatric Formulations, a WHO-hosted network

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Despite progress in reducing neonatal and child mortality, access to age-appropriate medicines remains inequitable, particularly in low-income and middle-income countries. The Global Accelerator for Paediatric Formulations (GAP-f), a WHO-hosted network established in 2020, addresses these gaps by uniting 33 partners to promote innovation and access to child-friendly formulations. Phase 2 (2022–24) of GAP-f's work focused on therapeutic areas where innovation and access efforts often did not have stakeholder alignment and coordination of designing and implementing innovative clinical trial methodology, engaging with regulators to address systemic barriers, identifying novel technologies for safe and effective delivery, and collaborating across stakeholders for product roll out. Learnings from GAP-f work include the need to adapt prioritisation processes to diverse therapeutic areas and focus on high-impact areas based on unmet needs. Platform trials emerged as a promising tool to accelerate evidence generation but require guidance from regulators, collaboration among pharmaceutical companies, and operational challenges and funding constraints to be overcome. Incentivising paediatric formulation development remains crucial for small volume paediatric markets, and efforts are also needed to more proactively enhance, accelerate, and effectively match innovations to deliver medicines to children more efficiently. Even when products are successfully developed, political will and community engagement are essential to creating demand, supporting roll out, and ensuring equitable access and appropriate use in children. Dedicated funding and targeted programmes are crucial to drive systemic and sustainable change. GAP-f implementation lessons discussed in this Personal View will inform the future of this needed initiative, accelerating progress towards improved medicines for children.

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Introduction

Despite advances in reducing neonatal and child mortality, children still face inequitable access to appropriately designed medicines, which endangers their health. Children need formulations that are dose appropriate, palatable, and easy to administer by caregivers, to reduce pill burden and ensure compliance. However, appropriate paediatric medicines are often non-existent, unavailable, costly, of inadequate quality, or have insufficient stability, especially in low-income and middle-income countries (LMICs).[1]

Over the past two decades, WHO has urged governments and drug developers to make newly approved medicines for adults also available for children, where appropriate.[2] Regulatory agencies in the USA and Europe have also imposed mandates and offered incentives to encourage investigation of novel medicines in children. A recent European Medicines Agency (EMA) analysis found that while these incentives did increase the number of medicines available for children after several years, medicines development remains driven by adult needs, and important paediatric priorities remain unaddressed, such as medicines for infants and treatment of children's cancers.[3] In 2021, only 7% of research and development at global pharmaceutical corporations addressed the needs of children younger than 12 years.[4]

Paediatric formulations are often developed years after adult formulations, with children sometimes waiting up to a decade for suitable treatments. Conducting clinical research in paediatric populations is particularly challenging due to insufficient capacity and the absence of harmonised regulatory guidance.[5] Moreover, poor forecasting and little pooled demand for paediatric

Key messages

1. Global Accelerator for Paediatric Formulations (GAP-f) is a WHO-hosted network created to respond to the paediatric formulations gap using an ecosystem approach to drive sustainable impact. Partnership with 33 stakeholder organisations has resulted in several achievements across the product lifecycle spanning various disease areas, through streamlining efforts to reduce inefficiencies.
2. Clarity on target product profiles and key priorities for development requires tailored assessment of epidemiology, market dynamics, and service delivery models.
3. Paediatric platform trials show the potential of adaptive designs to expedite evidence generation and optimise investments. These platform trials can be refined with input from regulators and industry, supported by long-term financing.
4. Initiatives such as the GAP-f Paediatric Technology Hub are needed to spearhead identification and application of key technologies to deliver medicines to children more efficiently.
5. Political commitment and active community involvement are essential to create demand and support safe and efficient medicine roll outs. Sustainable financing mechanisms are crucial in supporting paediatric medicine development, addressing market gaps, and ensuring timely access to essential medicines.
6. Building on lessons learned, GAP-f is well equipped to move into its next strategic phase of implementation, providing a needed mechanism that can help ensure availability of better medicines for children.

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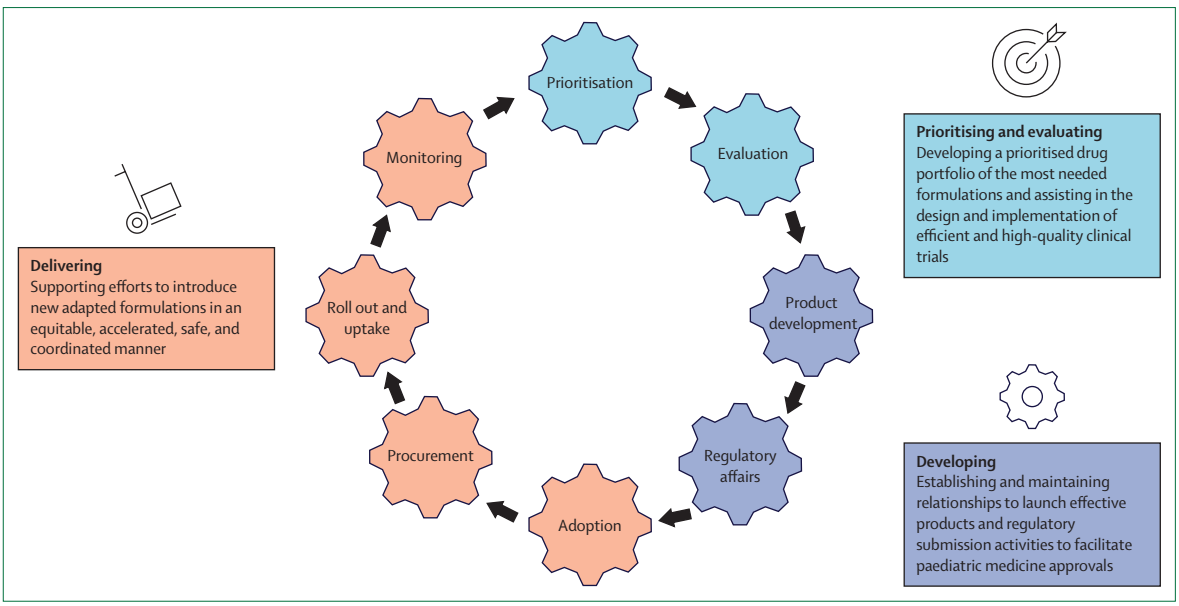


Figure 1: **Global Accelerator for Paediatric Formulations formalises collaborations across sectors to ensure accelerated development and uptake of the most needed drugs and formulations for children[1]**

medicines diminishes incentives for innovation and manufacturing. Together, these factors, combined with misaligned funding across the product development lifecycle, have delayed progress considerably.

A major challenge lies in the fragmented and often poorly coordinated efforts to address paediatric health priorities. The absence of setting global priorities has resulted in uncoordinated initiatives and funding shortfalls. The key stakeholders active in the field of paediatric medicines are research institutions and networks (eg, International Maternal Pediatric Adolescent AIDS Clinical Trials Network, Paediatric European Network for Treatment of AIDS, and the European Society for Paediatric Oncology), pharmaceutical companies, product development partnerships (eg, Drugs for Neglected Diseases Initiative, Medicines for Malaria Venture, Global Antibiotic Research and Development Partnership, TB Alliance, and Clinton Health Access Initiative), regulators (eg, US Food and Drug Administration and EMA), policy makers (eg, WHO), health-care providers and their associations (eg, Paediatric Adolescent Treatment Africa), civil society and community-based organisations (eg, Treatment Action Group), and funders (eg, governments and philanthropists). These stakeholders have made remarkable strides in their respective areas of intervention, but have often concentrated on distinct segments of the research, development, and access continuum, missing opportunities to break silos and fully address the product lifecycle.[6]

In response to these challenges, and backed by political commitment to do so, the Global Accelerator for Paediatric Formulations (GAP-f) was launched to advance the 2016 World Health Assembly resolution,[7] which emphasised the need for innovation and access to quality, safe, effective, and affordable medicines for children across the product lifecycle (figure 1). Established as a WHO network, GAP-f aims to expand partnerships and address paediatric formulations gaps by focusing on a broad spectrum of therapeutic areas. Currently, 33 partner organisations[8] are actively engaged, collaborating across four technical working groups on prioritisation, clinical research, product development and regulatory affairs, and product access and treatment delivery.[9] Membership comprises intergovernmental organisations, non-governmental organisations, product development partnerships, philanthropic foundations, and academic institutions. Each member organisation contributes to one or more of the working groups by participating in the implementation of the groups' strategy. A stakeholder engagement forum with four dedicated dialogues allows the network to actively engage with funders, industry, regulators, and civil society.

In March, 2022, GAP-f launched its 3-year phase 2 strategy (2022–24),[9] supported by multiple donors and stakeholders. Phase 1 (2020–21) served as the start-up phase and concentrated on addressing HIV, hepatitis C, and tuberculosis. Building on initial insights gained, GAP-f expanded its scope for phase 2 to tackle three additional disease areas including childhood cancers, neglected tropical diseases, and bacterial infections.

In this Personal View, we present key insights and lessons learned from GAP-f's implementation during its latest strategic period (2022–24). We outline the challenges encountered, highlight emerging opportunities, and identify potential areas for future engagement to optimise GAP-f's impact as an overarching mechanism aimed at

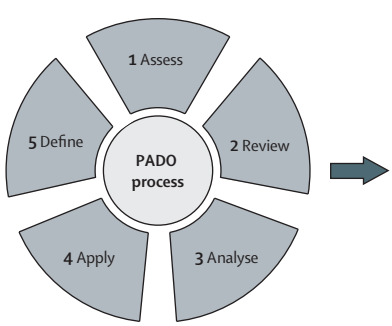
expanding access to essential paediatric medicines in adapted formulations.

Prioritising research and development efforts for targeted effect

Prioritisation has been a foundation of GAP-f work since inception.[10] Setting clear priorities is the first step to enable a targeted research and development approach, and creating a portfolio of the most needed formulations for children has been GAP-f's core priority. This prioritisation has helped direct the efforts and resources of researchers and manufacturers, focusing on optimal dosage forms to address the most urgent needs of children.

Paediatric drug optimisation (PADO) exercises have convened a broad variety of stakeholders (such as researchers and clinicians, implementing partners, market-shaping entities, and funders) and promoted discussions on needs and gaps to identify key priority products within each disease area and their preferred product characteristics for research and development. PADO-related activities had already been successfully undertaken by WHO, before the formalisation of GAP-f in 2020, for HIV,[11] hepatitis C,[12] and tuberculosis,[13] demonstrating their impact on guiding efforts of developers and funders to focus on priority formulations. To support similar processes in other disease areas, GAP-f developed guidance for undertaking a PADO process[14] that describes the overarching principles of a PADO exercise, the preparatory work required to inform the process, as well as how to adapt it across therapeutic areas. Through PADO processes, several core drug optimisation principles are applied, including the need to consider current gaps in access and market dynamics, and a long-term view that keeps pace with the evolving research and development landscape in adults.

Over the past 3 years, WHO and GAP-f partners have applied PADO processes to neglected tropical diseases,[15] antibiotics,[16] childhood cancers,[17] and COVID-19[18] (figure 2; panel 1). These efforts required substantial background assessment (including age-appropriateness of existing formulations and thorough documentation of the drug pipeline for any given disease) and adaptation of the tools to fully capture the diversity of each therapeutic area in terms of clinical management, service delivery, procurement, supply, and research and development landscape. This work represents an



		Priority list (next 3–5 years)	Watch list (next 5–10 years)
Antibiotics		Amoxicillin–clavulanic acid	Cefepime–taniborbactam
		Nitrofurantoin	
		Azithromycin	Sulbactam–durlobactam
		Cefiderocol	
Cancer		Cyclophosphamide (SDF)	Rituximab (subcutaneous)
		Etoposide (SDF)	
		Mercaptopurine (ODF)	
		Methotrexate (ODF or intrathecal)	Venetoclax
		Procarbazine (SDF)	
		Temozolomide (SDF)	
COVID-19		Nirmatrelvir–ritonavir	NA
		Tocilizumab	
		Baricitinib	
Neglected tropical diseases	Human African trypanosomiasis	Acoziborole (320 mg ODF)	
	Scabies and onchocerciasis	Ivermectin (1 mg or 1·5 mg ODT)	Emodepside
		Moxidectin (ODF)	Oxfendazole
	Schistosomiasis	L-praziquantel (150 mg ODT)	NA
		L-praziquantel (300 mg scored ODT)	
	Visceral leishmaniasis	Miltefosine (20 mg SDT)	LXE408
		Amphotericin B (SDF)	
Tuberculosis		Rifapentine (150 mg SDT)	All compounds in, or shortly entering, phase 2, specifically those that are more advanced in development (phase 2B/C);* long-acting technologies (eg, injectables or microarray patches) for tuberculosis medicines; oral dispersible film or strips of products that include rifapentine
		Rifampicin (100 mg SDT, tentative)	
		Moxifloxacin (100 mg dispersible tablet)	
		Pretomanid	

Figure 2: **Outcomes of WHO-led PADO processes across an expanded set of therapeutic areas**
ODF=oral dosage form. ODT=orodispersible tablet. SDF=solid dosage form. SDT=scored dispersible tablet. NA=not applicable. PADO=paediatric drug optimisation. *Including delpazolid, sutezolid, GSK-656, quabodepistat, BTZ-043, and TBI-223.[10]

important achievement of WHO and GAP-f partners, providing clarity in therapeutic areas where research and development efforts had often been conducted without the necessary alignment among stakeholders.

PADO exercises are designed to strategically connect with other WHO drug optimisation and normative functions, such as clinical guideline development, drug prioritisation exercises for adults, products prequalification, and updating of the model lists of essential medicines. PADO exercises have aimed to anticipate the future evolution of WHO guidelines based on limited, but growing, evidence on novel molecules and combinations typically investigated first in the adult population. In addition, the GAP-f assessment of age appropriateness of formulations listed on the WHO Model List of Essential Medicines for children (EMLc) has provided a key starting point to inform and guide PADO processes towards addressing relevant unmet needs.[19] A survey undertaken by GAP-f to assess the perceived needs of pharmacists and clinicians around the world was pivotal to increase our understanding of the limitations of existing marketed formulations.[20] This survey contributed to a larger body of work[19] that informed the optimisation of the EMLc[21] and set important foundations for future PADO exercises, while also establishing standards (eg, on palatability, acceptability, and ease of use in different health settings) for future EMLc applications.[22]

To ensure that PADO priority lists generated the desired effect, clear target product profiles were defined for antibiotics[23] and childhood cancer medicines.[24] The development of target product profiles by WHO and GAP-f partners has required substantial technical work to explore novel dosing approaches to simplify and harmonise weight-band dosing across diseases (eg, antibiotics, hepatitis C virus, HIV, malaria, and tuberculosis) and inform dosage forms that maximise flexibility across the age and weight spectrum.[25] Combined, these activities have offered concrete opportunities to innovate and optimise the way legacy drugs are used, while promoting harmonisation for pipeline products moving forward.

Panel 1: Lessons learned from applications of the paediatric drug optimisation process across various therapeutic areas

Neglected tropical diseases[15]
A limited drug pipeline heavily reliant on donation programmes required consideration of access and a holistic view across the product lifecycle, as well as considering an evolving funding and programme implementation landscape

Antibiotics[16]
The need to account for diverse ecology and epidemiology between adults and children was highlighted, emphasising the importance of tailoring prioritisation exercises towards unmet paediatric needs for which different compounds might be needed

Childhood cancers[17]
Medicines and formulations with multiple indications and therapeutic regimens required attention to combine specialised clinical management with a public health approach, while attempting to simplify therapeutic options and anticipate a fast-changing drug pipeline

COVID-19[18]
The need to quickly adapt drug optimisation principles in environments where the research and development landscape is highly unpredictable and rapidly evolves with epidemic changes was highlighted

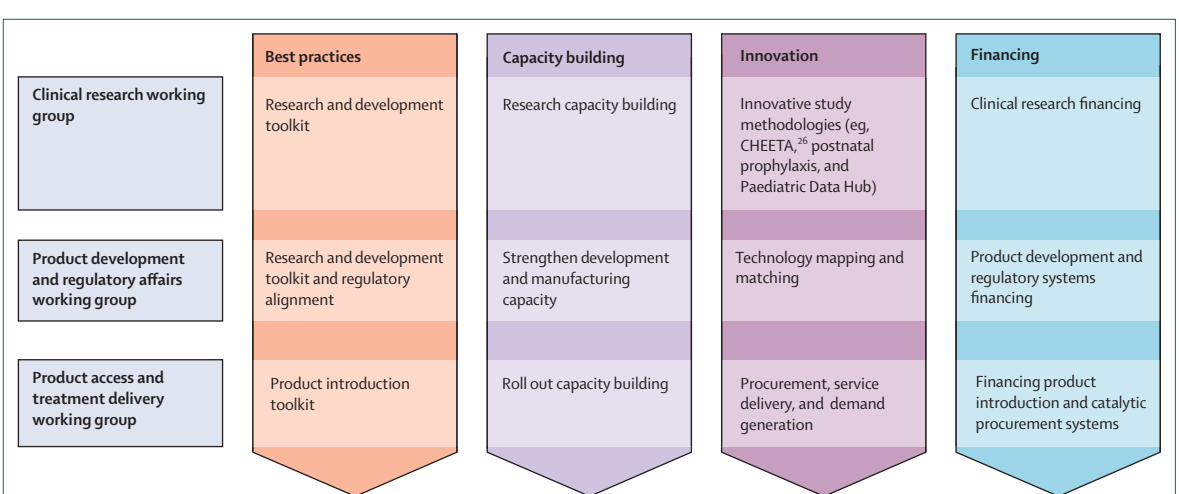


Figure 3: **Areas for acceleration to focus the collaborative efforts of the GAP-f network**
GAP-f brings together approaches to research, development, and delivery efforts for medicines for children that can be applied across therapeutic areas and products. The work involves applying lessons learned to build enabling policies and guidelines and, where needed, develop specific technical toolkits for acceleration.[1] GAP-f=Global Accelerator for Paediatric Formulations.

The maintenance of an updated portfolio of priority paediatric products will be a cornerstone of GAP-f output moving forward, to ensure that collaborative efforts target the diseases with the greatest unmet public health need. The future prioritisation framework will require consideration of therapeutic areas in which the greatest effect can be achieved, based on GAP-f strengths and expertise in the context of ongoing initiatives, resources available, and stakeholder landscape.

Accelerating evidence generation to inform optimal drug development and use

Many lessons have been learned from the work of GAP-f in clinical research that aimed to support accelerating evidence generation to inform optimal drug development and use (figure 3). Building on the strong expertise of network members who have led paediatric clinical research for several diseases, especially infectious diseases, GAP-f focused on the design and implementation of innovative clinical trial methods, as well as opportunities to access the potential of real-world evidence.[27]

The design and implementation of platform trials have generated particular interest among GAP-f members as the experience from trials of COVID-19 therapeutics showed that adaptive strategies could help expedite studies of novel and repurposed agents.[28] Such adaptive platform trials to compare multiple novel treatment strategies for neonatal sepsis (SNIP-AFRICA) and infant postnatal HIV prophylaxis (RISE UP)[29] are now using this approach (panel 2). Clinical research platforms to run single-arm studies that use existing infrastructure, such as in the case of the PETITE-X and CHEETA platforms (panel 2), are also under development. In all these cases, expertise, enrolment, capacity, and

For more on **SNIP-AFRICA** see https://www.snip-africa.org

Panel 2: **Key studies and study concepts led by Global Accelerator for Paediatric Formulations (GAP-f)**

Research on Innovative Strategies for Ending HIV Transmission and Universal virologic suppression in mothers (RISE UP) trial

New antiretrovirals, especially long-acting formulations, have the potential to eliminate newborn transmissions, either as maternal treatment or as postnatal prophylaxis. Built on the output from 2 years of workshops facilitated by GAP-f and the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) network,[30] RISE UP[29] has been designed as a pragmatic platform trial to study the latest antiretrovirals, including long-acting formulations. Mothers with HIV at risk for viremia and their infants will be randomly assigned to intervention groups testing maternal treatment or infant postnatal prophylaxis, or to a reference standard of care. The primary endpoint will be the rate of vertical transmission, and the trial will also generate rigorous and generalisable evidence about effectiveness more broadly, along with information about costs, safety, quality of life, feasibility, and acceptability. GAP-f has had a key role at multiple stages of RISE UP. The idea for this trial arose from a postnatal prophylaxis workshop, organised and partially funded by GAP-f. GAP-f also linked investigators from the IMPAACT and PENTA trial networks to apply jointly for a European & Developing Countries Clinical Trials Partnership funding opportunity. GAP-f also facilitated multiple technical discussions with industry representatives from multiple disease areas and regulatory agencies in various jurisdictions. In particular, GAP-f provided a platform to explore the regulatory environment and made regulators more aware of feasibility challenges attached to traditional clinical trial approaches.

Chasing Expedited and Equitable Treatment Access (CHEETA) for children with tuberculosis

To shorten paediatric tuberculosis medicine evaluation delays, the CHEETA team designed a platform trial approach to implement phase 1/2 paediatric studies focused on pharmacokinetics, dose-finding, and safety of tuberculosis drugs in children to support regulatory approval and policy change. The platform, with leadership from Stellenbosch University and Treatment Action Group, will rely on existing and newly capacitated clinical trial sites in countries with a high burden of tuberculosis and use a common protocol designed with input from regulators. The CHEETA team has been providing a forum to gather paediatric tuberculosis trialists and provide early input to innovators on formulation and trial design that would otherwise be unavailable. The GAP-f network offered strong thought-partnership regarding platform design applied to other therapeutic areas, as well as a strategic perspective into how to foster engagement with the private sector, regulators, and funders. Connections with other researchers throughout the GAP-f network has enabled the CHEETA team to vet these concepts while benefitting from lessons learned and expertise from researchers outside tuberculosis.

PETITE-X

This research platform is dedicated to accelerating the assessment of the latest HIV medicines and novel paediatric formulations in term and preterm neonates. PETITE-X builds on an ongoing collaboration between Stellenbosch University in South Africa and Chiang Mai University in Thailand. Since establishment in 2020, the PETITE platform has performed three studies on antiretrovirals in neonates exposed to HIV: PETITE4-in-1,[31] PETITE-ABC/3TC-LPV/r,[32] and PETITE-DTG.[33] Of particular awaited interest is the first assessment of an antiretroviral oral dispersible film formulation of dolutegravir. Through the GAP-f network, the PETITE team had the opportunity to interact with key partners and stakeholders to design a disease agnostic PETITE-X research platform and apply the lessons learned to knowledge gaps from other diseases areas. The programme is expected to expedite the delivery of clinical trials of anti-infective medicines for preterm and term neonates, thus supporting regulatory approvals, label extension, new indications, and guideline revisions.

For more on the **VERDI project** see https://verdiproject.org

infrastructure are maximised to accelerate evidence generation and optimise investment. Although some of these approaches are increasingly being adopted, several challenges have been gathered through GAP-f's work: regulators have expressed some reluctance towards the use of data from adaptive platform trials for regulatory purposes; pharmaceutical companies have had little interest in joining comparative studies assessing competitor products; and investments are needed to align trial procedures, anticipate forthcoming compounds characteristics to future-proof trial design, and minimise protocol amendments. These lessons will guide GAP-f work to further streamline innovative study designs and promote their use for paediatric investigation of novel therapeutics.

The work of GAP-f on clinical trial efficiency has also highlighted existing opportunities to strengthen the ecosystem of clinical trials for paediatric drug approval and use. For example, work on the CHEETA platform (panel 2) has generated useful mapping of clinical trial capacity in countries with high tuberculosis burden and has flagged capabilities that could be used for other diseases. Integration of clinical trial networks within a so-called network of networks might provide future opportunities to expand and foster clinical trial capacity and enable faster enrolment and completion of clinical trials that are key for approval and use of novel medicines. This work connects and synergises with global efforts resulting from a World Health Assembly resolution on strengthening the clinical trial ecosystem and supporting a more equitable environment for studies to be done in affected communities and underserved populations.[34]

The SNIP-AFRICA and RISE UP studies use novel statistical methods (ie, Bayesian methods and practical design;[35] panel 2) to tackle the challenge of designing well powered clinical trials and minimise enrolment requirements, which remains an issue especially for rare paediatric conditions, such as some childhood cancers. Innovative investigational methods to allow meaningful interpretation of data from trials of small size alongside collection and analysis of robust real-world evidence is likely to be fundamental to addressing this issue. For example, in the event of drug repurposing against an emerging infectious disease, extrapolation of safety and dosing data from previous approvals or real-world data in paediatric populations will expedite clinical efficacy studies.

The GAP-f Paediatric Data Hub[36] was designed as a mechanism to facilitate the monitoring of new paediatric formulations as they are rolled out globally and, where needed, to inform related regulatory processes. Through the Paediatric Data Hub, WHO and GAP-f partners will work collaboratively to define priority research questions, identify appropriate data sources, and promote innovation and best practices for optimal data sharing and analysis. GAP-f's foundational work on the Paediatric Data Hub highlighted substantial disparities between existing data systems in countries and the potential of data pools and standardised routine monitoring systems. Data sharing policies and data quality remain considerable hurdles, but several initiatives,[37] such as the VERDI project, have provided examples of how these challenges could be overcome to inform drug approvals and introduce safe use of novel medicines. Engagement with regulators, country programmes, and pharmaceutical companies will be essential in the future to fully articulate a vision for evidence generation in which clinical trial and real-world datasets can be integrated and complement each other in the context of existing standards for high-quality research.

Exploring regulatory efficiencies for accelerated innovation and increased uptake

The GAP-f work towards optimal study design described above has considered existing regulatory frameworks, with active engagement of key members of regulatory agencies such as the US Food and Drug Administration and EMA. This collaboration has helped GAP-f partners appreciate and acknowledge the crucial role that paediatric regulatory frameworks have had over the past 20 years, without which paediatric investigation of several novel therapeutics would have not happened.[38] However, our work has also highlighted several opportunities for stronger alignment among agencies as well as the need for pragmatism when novel solutions are urgently needed, such as in the case of neonatal sepsis. Using WHO's convening role and the expertise of GAP-f members on paediatric regulatory matters, technical consultations were organised to discuss specific themes associated with approval and use of novel therapeutics in HIV and antibiotics where a mismatch between public health needs and current regulatory frameworks were identified. These consultations included exploring ways to streamline a regulatory pathway for novel antiretrovirals that could be used for HIV postnatal prophylaxis (unplublished), and identifying risk-based approaches for investigation of novel antibiotics and approval for conditions that are aligned with neonatal and paediatric medical needs.[39]

GAP-f partners successfully engaged with regulators on technical discussions, increasing our shared understanding of the barriers to regulatory studies implementation and reflecting on alternative approaches to better address those unmet public health needs in paediatric populations. One next step is the development and piloting of a unified plan for evidence generation that could be designed with WHO and GAP-f facilitation to foster regulatory alignment and optimise clinical development plans towards an evidence package that would satisfy regulatory requirements across jurisdictions. This work will make use of recent developments such as the release of International Council of Harmonization (ICH) guidelines on paediatric extrapolation in

August, 2024, that pave the way for harmonisation of the concept of extrapolation globally.[40]

The revamping of the WHO-convened Paediatric Regulatory Network[41] also gave WHO and GAP-f partners multiple opportunities to engage with a broader set of national regulators (eg, Ghana Drugs and Herbal Medicine Registration Food and Drugs Authority; Health Canada; Indonesian Food and Drug Authority; Nigerian National Agency for Food and Drug Administration and Control; Pharmaceuticals and Medicines Devices Agency Japan; South African Health Products Regulatory Authority; and Swissmedic). Engagement with the Paediatric Regulatory Network also allowed for reflection on tools that can accelerate national approvals and product introduction, such as reliance mechanisms, including the WHO Collaborative Procedure for Accelerated Registration[42] and regional collaborations. Challenges remain in finding balance between promoting national regulatory sovereignty and simplifying regulatory submission pathways for manufacturers that often have few incentives for a broad regulatory strategy across regions with different requirements and processes. Further work in this area will be required as GAP-f considers its new strategic period.

Overall, GAP-f work in the regulatory space has largely focused on systemic issues that will likely require years to be fully resolved. In the meantime, support to product-specific pathways is also being provided. Best practices have been identified and continued work is required to condense these into a replicable set of principles to be applied more broadly.

Opportunities and challenges to develop paediatric formulations and innovate drug delivery platforms across diseases

The little amount of commercial incentives for pharmaceutical companies to develop paediatric formulations is a long-standing issue largely driven by the small markets that children represent across several therapeutic areas. GAP-f partners have learned from recent experiences with treatment for HIV (ie, paediatric dolutegravir)[43] and tuberculosis (paediatric rifapentine)[44] that incentives can be designed to facilitate technology transfer, begin development, support regulatory submission, provide volume guarantees, and generate demand. With the enabling role of GAP-f, generic fixed-dose formulations, such as those combining abacavir, lamivudine, and dolutegravir and darunavir with ritonavir, were developed under the leadership of the Clinton Health Access Initiative and the financial support of Unitaid, who also started work on fixed-dose combinations containing tenofovir alafenamide. However, replicating those success stories in other disease areas is not free of challenges, as GAP-f experienced with hepatitis C. To date, despite foundational work on pharmacokinetic modelling,[45] designing clinical studies, exploring regulatory pathways, and sizing the market, a paediatric formulation of sofosbuvir 100 mg (to combine with daclatasvir in a pan-genotypic regimen to cure hepatitis C) does not exist. This product's small and unattractive market would have required an incentive programme that GAP-f could not mobilise financial support for, despite broad outreach to donors, which resulted in the workstream being put on hold and a missed opportunity to cure half a million children living with hepatitis C. This case study highlights that sometimes even limited resources are essential to launch and accelerate the development of paediatric products, and that equitable access to therapeutic solutions can only happen through targeted and catalytic investments in this space.

Even when paediatric products are developed, few new drug formulations and delivery technologies (eg, oral films, microarray patches, and oral and injectable nanotechnologies) get considered for paediatric application. When these new formulations and technologies are considered, there are numerous delays to their development until they become available. Although prioritisation has been well applied to active pharmaceutical ingredients across disease areas through PADO processes, no such mechanism exists to prioritise and drive innovation in new drug delivery technologies for paediatric use. The consequences of no proactive prioritisation of formulation technologies are exacerbated by limited resources to fund innovation of drug delivery platforms and shortcomings in public health budgets to afford such new technologies. To fill this gap, a GAP-f Paediatric Technology Hub has been designed to provide guidance on desired formulation attributes of prioritised medicines, and foster cross-functional collaborations among formulation scientists. The Paediatric Technology Hub will systematically identify promising existing and emerging technologies for potential paediatric use; assess their suitability, feasibility, and appropriateness to satisfy diverse disease needs for paediatric populations (eg, aspects specific to implementation in high-burden settings, including transport, storage, and delivery in hot or humid climates); and inform matching of optimal dosage forms and formulations with PADO-prioritised active pharmaceutical ingredients, at times complemented with enabling studies to advance and de-risk priority product development (figure 4). A database will support broad dissemination of technology characteristics, including results of analysis of suitability and feasibility led by GAP-f partners.

Improving delivery of paediatric medicines through coordinated and collaborative approaches

When paediatric formulations are developed, access to these products is not assured. Recurrent shortages of paediatric formulations of common medicines have been well documented (especially in high-income countries).[46] A range of factors might complicate reliable access, including limited surveillance, unreliable forecasting,

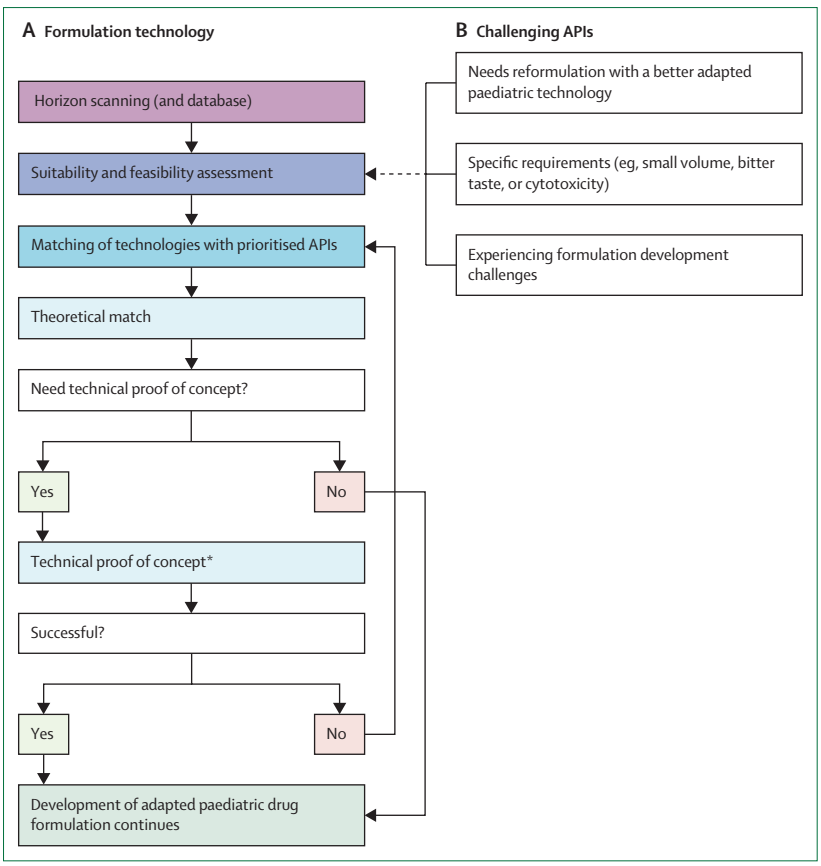


Figure 4: **GAP-f Paediatric Technology Hub**
The Paediatric Technology Hub includes three workstreams: horizon scanning, suitability and feasibility assessment, and matching of technologies with APIs. The Paediatric Technology Hub provides two starting points: formulation technologies that are assessed, short listed, and evaluated for matching with PADO-prioritised APIs (A) and APIs needing reformulation, having specific requirements, or experiencing formulation development challenges, aiming to find an appropriate technology to address those challenges (B). APIs=active pharmaceutical ingredients. PADO=paediatric drug optimisation. *The workflow includes optional technical proof-of-concept work to confirm theoretical matches and decrease risk in the continued development of adapted paediatric drug formulations.

small and fragmented markets, slow planning and patient engagement, and suboptimal coordination of procurement within and between countries.[47] Small profit margins might further threaten reliable supply. Unlike HIV, tuberculosis, and malaria, no large donors exist to support product transition and uptake in most other therapeutic areas.

The GAP-f network has taken a collaborative approach to enabling better access to paediatric formulations (figure 3) through a platform for coordination and collaboration across stakeholders. Information sharing and coordination at all levels of implementation has driven GAP-f's Paediatric Dolutegravir Task Team, which has contributed to seamless and swift uptake of paediatric dolutegravir for HIV treatment, building on catalytic procurement and strong uptake support from various agencies. This coordination included the development of guidance, a brief, and a toolkit that has contributed to accelerating access to paediatric dolutegravir.[48] The slow transition to the paediatric abacavir, lamivudine, and dolutegravir fixed-dose combination, which has the potential to support simplified procurement, improve adherence, and result in better health outcomes for children, has underscored the importance of proactive and timely coordination supported by technical advocacy, including on implementation guidance (ie, forecasting, quantification, procurement, and introduction).[49]

Key enablers to paediatric formulations

Lessons learned from GAP-f's product access and treatment delivery work have been captured by network partners in a toolkit to support new product introduction and rapid roll out at scale.[50] Effective and timely collaboration between pharmaceutical originators and generic manufacturers is a key enabler of access to paediatric formulations. Instruments such as public health-focused voluntary licensing agreements can expedite access to medicines of important public health value[51] and need to be considered early in the development process. These instruments should be used to increase affordability for governments and reduce direct expenditures for patients. Although competition between manufacturers might be beneficial to contain prices, the number of manufacturers to engage needs to align with anticipated demand to ensure sustainability.

Preparing for robust uptake of paediatric formulations through strong political engagement with dedicated funding mechanisms requires using domestic funding and development assistance, and shaping local paediatric drug markets to reduce fragmentation and optimise paediatric drug availability for inclusion in essential health service commodity packages.[5]

Rapid in-country registration and proactive monitoring, such as the WHO Collaborative Procedure for Accelerated Registration, might facilitate and accelerate regulatory pathways and can aid access to paediatric formulations. Tracking detailed country-by-country information on regulatory approvals for new paediatric products has the potential to flag gaps in access to paediatric formulations and trigger actions to expedite access.[52]

Timely and well conducted quantification exercises at national and regional levels are essential for adequate ordering and ensuring effective supply chains that minimise wastages and stockouts. Pooled procurement mechanisms (such as those brokered by several international, regional, and national agencies) can maximise investments and ensure continuous access to paediatric drug products, most importantly in low volume markets.

Beneficiaries (ie, children and their caregivers) and other health-care cadres should be involved along the product usage pathway. Capacity-building initiatives help empower national actors and potentially make health-care systems simpler to navigate for children and their caregivers.

Communities that are aware of, and involved with, multiple stages of the product lifecycle, including national processes and decision making, can initiate change towards optimal child health outcomes.[53] The fundamental role that communities have in demand generation through direct advocacy, treatment literacy, and support to service delivery has been an essential lesson learned from HIV and tuberculosis paediatric drug optimisation and roll out. Integration of community-led monitoring strategies can track how services are experienced, and the factors that affect service access to improve service delivery or recognise challenges.[54]

Systems to collect data on drug safety and effectiveness when novel paediatric products are introduced are crucial to assess effect on health and ensure safe use of products. The GAP-f Paediatric Data Hub is a mechanism to use real-world data for monitoring drug safety and effectiveness, thereby complementing the WHO pharmacovigilance framework to strengthen safety monitoring systems in countries.

Strengthening collaborative engagement with stakeholders

Over the past three years, GAP-f has strengthened its engagement with stakeholders, fostering collaboration with funders, implementers, the private sector, regulatory bodies, civil society, and communities. To facilitate this engagement, GAP-f established a structured mechanism to regularly consult and promote collaborations with key stakeholders beyond its member organisations and disseminate outputs from the network, promoting inclusivity, shared responsibility, and political and financial mobilisation in shaping the paediatric medicines landscape.

Engagement led by GAP-f with the pharmaceutical sector through both bilateral and focused group dialogues aimed to align on priorities, exchange best practices, and uncover challenges. Topics such as small-volume procurement, platform trials, and adaptation of novel technologies and delivery methods for LMICs have been explored. These engagements yielded valuable insights, especially when involving targeted individuals with relevant expertise. Given the complexity and scale of many private sector organisations, GAP-f's efforts will increasingly require outreach to appropriate stakeholders who possess the authority and alignment necessary to drive the paediatric agenda forward. To address these challenges, GAP-f aspires to develop a comprehensive framework for formal engagement with the private sector. The framework will promote best practices and shared behaviours across the product lifecycle, fostering stronger collaboration and accountability between GAP-f members and industry stakeholders.

GAP-f has engaged with civil society and community organisations to mobilise political leadership to accelerate the introduction and roll out of improved medicines for children. As part of these efforts, GAP-f published an advocacy brief[55] to help align, support, and mobilise advocacy around accelerated access to safer, more effective, and quality-assured medicines in optimal paediatric formulations. This brief included messages around focusing on priority drugs in the pipeline, strengthening coordination for faster access, addressing regulatory challenges to incentivise research and development, ensuring sustained access to affordable medicines, and mobilising resources for better paediatric formulations. Although some therapeutic areas (such as HIV and tuberculosis) have vigorous civil society and community advocate networks, both globally and across LMICs, there are several other therapeutic areas or regions where community engagement remains minimal.

To improve alignment on global health priorities and funding opportunities for priority paediatric medicines, GAP-f has engaged with WHO member states through bilateral engagements, high-level events at the World Health Assembly, and dedicated briefings. A noteworthy outcome of these efforts has been the adoption of a World Health Assembly resolution[56] that underscores the urgent need to ensure access to age-appropriate medicines for children and calls on WHO member states, stakeholders, and the WHO Secretariat to accelerate efforts to do so. Achieving these goals requires increased accountability and sustained commitment from WHO member states; for instance, ensuring that national policies, such as essential medicines lists, are regularly updated to address the needs of paediatric populations. Moving forward, GAP-f will further collaborate with WHO member states and other stakeholders to foster shared responsibility and strengthen accountability mechanisms, driving long-term advancements in the paediatric agenda. One such effort will be to determine and promote the uptake of essential medicine lists in countries.

GAP-f has engaged with donors to provide visibility on funding gaps that might thwart progress and promote complementarity of funders in increasing resource allocation. Although this effort has been well received, a crucial challenge persists in navigating the post-pandemic and current geopolitical funding environment marked by reduced resources, competition across multiple initiatives, and a misconception that the paediatric health landscape is sufficiently funded. The current context underscores the importance of targeted efforts and donor alignment on identified priorities (such as priority products and research gaps identified from PADO processes) and coordination among funded projects, avoiding duplicative efforts and eliminating funding gaps that can halt progress along the product lifecycle. Catalytic investments will continue to remain essential to tackle the market failure of many paediatric formulations; however, such investments will not entirely address the systemic changes required across therapeutic areas. Achieving sustainable progress to ensure availability of paediatric formulations in countries will require political will, domestic financing,

the use of effective pooled financing mechanisms (eg, multipartner trust funds), innovative financing models, or existing global financing tools (eg, Global Financing Facility) that have proven to address historical funding shortcomings to maximise effectiveness.

Conclusion

GAP-f has shown the potential to align and mobilise diverse stakeholders to accelerate research, development, and delivery of child-friendly formulations for the most needed medicines. A well coordinated network allows for more to be achieved with efficient use of limited time and resources. Existing frameworks and mechanisms should be coordinated, used, and actively enabled to fast-track research, product development, regulatory approval, introduction, and monitoring.

The experiences and lessons from GAP-f's phase 2 strategic period are pivotal in shaping GAP-f's future trajectory, building on strengths and adopting a more targeted and impactful approach. In the next strategic phase, GAP-f will expand its focus to encompass a wider range of therapeutic areas, guided by a prioritisation framework driven by disease burden, unmet needs, and stakeholder and funding landscapes to identify where GAP-f interventions can be most effective. Priority areas for initial focus will include malaria, sickle cell disease, epilepsy, and respiratory syncytial virus.

GAP-f's future efforts will align with, and contribute to, global initiatives such as those linked to the WHO resolution to strengthen the clinical trials ecosystem,[34] which will foster a more equitable environment for studies in underserved populations. Engagement with global regulators and pharmaceutical companies will be central in articulating and implementing more integrated evidence generation approaches, in which high-quality clinical trial data and real-world evidence complement each other. The GAP-f Paediatric Technology Hub will foster cross-functional collaboration to match emerging technologies with priority active pharmaceutical ingredients and reduce the time until children benefit from medical innovation. By advancing and de-risking paediatric formulations development, GAP-f will accelerate the delivery of life saving, child-friendly products, particularly for high-burden settings. Looking ahead, GAP-f's growing engagement with civil society and communities, regulators, funders, industry, and WHO member states will be directed at fostering an ecosystem approach and creating an enabling environment that increases impact of ongoing efforts and increased investments across the product lifecycle.

Diversifying, expanding, and consolidating funding will remain an urgent need for GAP-f and its members in order to achieve these goals, and targeted, strategic, and innovative investments can transform the paediatric medicines landscape and take us to a future where no child is left in need of essential medicines to survive and thrive.

Contributors

MP conceptualised and outlined the Personal View, which was then reviewed by all authors. MP and AH wrote the first draft with considerable contribution from SM. FM, TR, TRC, and JC contributed to specific sections of the manuscript. All authors reviewed, edited, and agreed with the final version of the submitted manuscript. We accept sole responsibility of the content of this manuscript, which does not represent the official views of WHO.

Declaration of interests

We declare no competing interests.

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