*We all have a role to play…*

# What will it take to achieve equitable access to essential medicines & equipment for the global Congenital Adrenal Hyperplasia (CAH) Community?

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## A briefing paper for the World Health Organisation


Prepared by @MATES4Kids

**(Maximising Access To Essential Supplies for Kids)**



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## Acknowledgements

In the spirit of reconciliation @MATES4Kids acknowledges the Traditional Custodians of Country throughout Australia and the connections of Aboriginal and Torres Strait Islander peoples to land, sea and community. In particular, we acknowledge the Wallumedegal Peoples of the Eora Nation, on whose land CLAN (Caring & Living As Neighbours) is headquartered. We pay our respect to Elders past and present and extend that respect to all First Nations leaders around the world.

@MATES4Kids acknowledges the international CAH Community and thanks the many community members, allies and experts who have contributed so generously to the development of this paper.

We thank Professor Garry Warne for allowing @MATES4Kids to use images from his ground-breaking book for families "*Your child with Congenital Adrenal Hyperplasia*". This book was first published in Australia in 1988 and has since been translated into multiple languages (including Vietnamese, Chinese, Bahasa Indonesia, Urdu, Tagalog, Dutch and French).

Warne's booklet was beautifully illustrated by Jocelyn Bell, and the images are used with permission throughout this paper (including the image on the front cover of this briefing paper, and Figure 1, below). An invaluable resource for families around the world, the booklet uses simple, lay language to communicate complex concepts, making them accessible to all. The messaging is full of hope, unity, encouragement and empowerment, and the booklet has been instrumental in strengthening the international CAH Community.

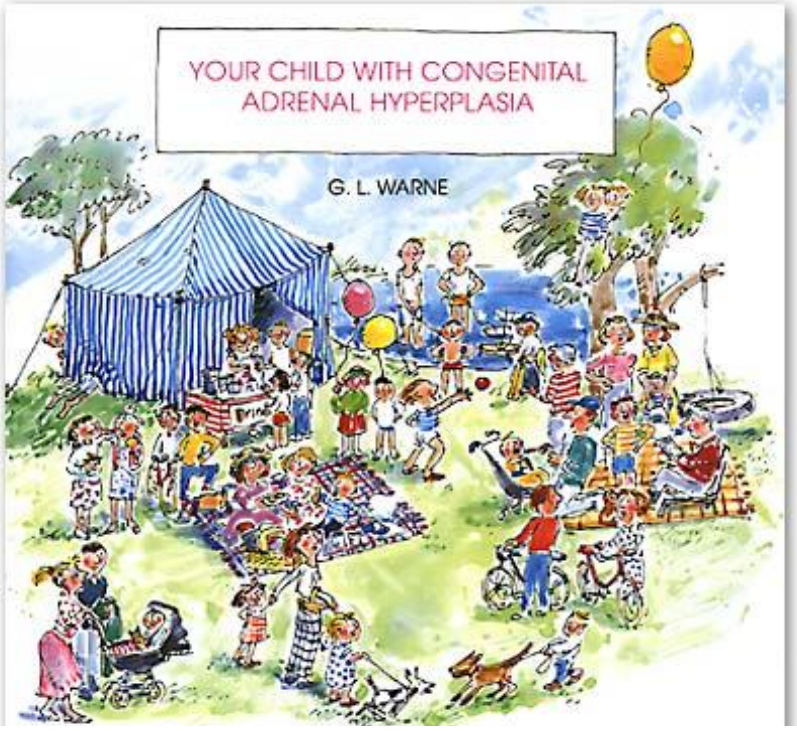


*Figure 1 – Cover image from "Your child with Congenital Adrenal Hyperplasia", a booklet written by Professor Garry Warne and illustrated by Jocelyn Bell in 1988.*

## Executive Summary

> *"It ought to be remembered that there is nothing more difficult to take in hand, more perilous to conduct, or more uncertain in its success, than to take the lead in the introduction of a new order of things. Because the innovator has for enemies all those who have done well under the old conditions, and lukewarm defenders in those who may do well under the new. This coolness arises partly from fear of the opponents, who have the laws on their side, and partly from the incredulity of men, who do not readily believe in new things until they have had a long experience of them."*
> Niccolò Machiavelli, The Prince

A baby born with Congenital Adrenal Hyperplasia (CAH) in a high-income country of the world today can be expected to enjoy a quality and duration of life on par with that of children born without CAH. CAH is now one of the most common inherited non-communicable diseases (NCDs) of childhood in high-income countries. Affected babies are diagnosed early by universal newborn screening programs, then commenced on highly effective, evidence-based treatment regimens with low-cost medications, hydrocortisone and fludrocortisone tablets, which are taken several times a day. Both of these medications are on the World Health Organisation's Essential Medicines List for Children.

By contrast, the vast majority of children born with CAH in low-income countries today will die. CAH remains a very rare condition in these countries due to inequitable and preventable infant mortality, and is increasingly acknowledged as contributing to the NCD burden amongst the poorest billion (Bukhman et al. 2020). Even those children lucky enough to be diagnosed during infancy will most likely die at an early age – but only after their parents have bankrupted themselves in futile efforts to affordably access the medicines and healthcare essential to keeping their children alive.

This gross inequity is unjust, and at odds with the United Nations' Convention on the Rights of the Child.

This gross inequity is also completely unnecessary. Collaborative actions internationally have clearly demonstrated change is possible if and when many stakeholders work together to benefit children living with CAH. Collective apathy allows the injustice to continue.

This briefing paper combines expertise, insights, data and examples from around the world to paint a detailed picture of the current circumstances and challenges facing the international CAH Community, and outlines a path forward for change. We present a specific request to the World Health Organisation to work with @MATES4Kids to develop an innovative forum. From such collaboration, strategic action will identify the critical, practical, scalable actions needed to redress inequities and optimise affordable access to the essential medicines and equipment needed by #EVERYchild living with CAH around the world if they are to survive and thrive.

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## Background

In 2004, Congenital Adrenal Hyperplasia (CAH) Support Group Newsletters in the United States of America (USA) and Australia shared stories of the health inequities experienced by the CAH Community of Vietnam. A member of the Australian CAH Community (Mrs Michelle Konheiser) and an Australian Paediatric Endocrinologist (Prof Garry Warne) had travelled to Vietnam, and, with the strong support of leading health professionals at the National Hospital of Pediatrics in Hanoi, met with members of Vietnam's CAH community.

Reports shared by Konheiser and Warne regarding what they heard and saw made for emotional reading in the international CAH Support Group Newsletters. Children and families in Vietnam were unable to affordably access the medicines and care they needed to survive and thrive, and children were dying and experiencing extreme morbidity, stigmatisation and social isolation to an extent unheard of in high-income countries.

In response to a direct request for help, collaborative action and multisectoral commitment in years since have dramatically changed the situation for the CAH Community in Vietnam. CAH medicines are now on the World Health Organisation Essential Medicines list for children (EMLc), the Vietnamese National EML and the Vietnamese insurance scheme; medicines are affordably available in Vietnam; national newborn screening for CAH is diagnosing children early; the Vietnam Pediatric Endocrinology Society is leading genetic research on CAH internationally; health professionals across the country are highly skilled and trained to diagnose and manage CAH; the CAH Community of Vietnam actively connects on Facebook; and the prevalence of CAH and health outcomes continue to improve.

Like a bad case of déjà vu, however, reports from Zimbabwe and Nigeria in 2021 indicate many families around the world continue to experience inequitable burdens associated with CAH due to ongoing challenges accessing affordable medicines, quality healthcare and appropriate equipment. While targeted action in each of these countries over the next decade would undoubtedly effect similar change to that seen in Vietnam so far, it will not be enough. Children in other low- and middle-income countries (LMICs) need change too.

If we are to reduce the preventable mortality associated with CAH by 30% by 2030 we need to do things differently. It is time to work together like never before, think big, and change the landscape for the global CAH Community. Such action will require multisectoral, collaborative action on an enormous scale. And yet, the childhood cancer and type 1 diabetes communities give us hope that such commitment and change is possible. It is time to come together, as mates, and improve access to CAH supplies and care for #EVERYchild.

## Snapshot of Inequity: Results of a global CAH survey by the IPA

The International Pediatric Association (IPA) conducted a survey in 2021 on access to essential medicines and equipment for patients with CAH, which included respondents (representatives of each country's national pediatric societies) from 14 countries across 7 regions:

- Asia Pacific (Indonesia, Malaysia, Singapore)
- Central Asia (Turkey)
- Europe (Kosovo, North Macedonia, Armenia)
- Middle East and North Africa (Jordan)
- Sub-Saharan Africa (Kenya, Botswana, Cote d'Ivoire)
- North America (Canada); and
- Latin America (Mexico, Costa Rica).

The survey found essential drugs and tests are still unavailable in some countries, further emphasising the need for continued advocacy for CAH patients.

- Fludrocortisone was available in only 9 respondent countries, *not* available in 2 countries (Cote d'Ivoire and North Macedonia), *sometimes* unavailable in Kenya, available "in the black market" in Indonesia, and unregistered but can be found in Armenia.

- Hydrocortisone was available in all respondent countries except Kenya, where "sometimes it's not available".

- Testing for 17-OHP was available in 10 countries, except North Macedonia, Cote d'Ivoire, Kenya, and Indonesia, in which 17-OHP tests were available in private laboratories only.

- The majority of respondent countries did *not* have a CAH newborn screening program available. The program was available in Singapore, Turkey, Canada, Mexico, and Costa Rica.

- Hydrocortisone for IV injections was not available to manage adrenal crises in Turkey and Armenia.

- Peer/support groups/communities for CAH patients were only available in 5 respondent countries (Indonesia, Singapore, North Macedonia, Canada, and Costa Rica).

The results of this brief survey highlight the pressing need of making medications, tests, and patient support accessible equally across the globe.

**The International Pediatric Association is a founding member of @MATES4Kids**

## An Introduction to @MATES4Kids

**"So, your child's been found to have CAH. Sounds terrible . . . but is it?**

*CAH is a fairly uncommon disorder, but one which is well understood and for which good treatment is readily available.* ***People with CAH enjoy excellent health once treatment has been started and live to a ripe old age. They can do anything they want to do, including marrying and having children. To maintain this state of good health, they do need to take medications, but this becomes accepted as part of life. The tablets are never in short supply and they don't cost a lot.*** *There are many conditions much worse than CAH.* ***CAH is a nuisance, but not a handicap. A support group of CAH patients, their parents and their friends exists to give you further assistance.*** *Your doctor can put you in touch with them."*

**Quote from "Your child with Congenital Adrenal Hyperplasia" written by Professor Garry Warne in 1988**

For decades now, life for children living with CAH in Australia and other high-income countries has been made easier by affordable access to the essential medicines hydrocortisone and fludrocortisone. Indeed, the international CAH Community has progressively grown in size, strength and connectivity, with support from a broad range of multisectoral allies (Armstrong et al. 2020).

Despite these achievements, equity has not yet been achieved for the international CAH Community. There still exist far too many countries with little or no affordable access to CAH medicines (Rowlands et al. 2021).

@MATES4Kids is a coalition of like-minded organisations and individuals committed to collaborative action aimed at identifying, implementing and monitoring practical solutions to improve access to essential medicines for the global CAH Community. We acknowledge the work of the World Health Organisation and United Nations to improve access to medicines and quality healthcare for all and welcome the upcoming Second United Nations High Level Meeting on Universal Health Coverage (UNHLM UHC) in 2023 and Fourth UNHLM on NCDs planned for 2025 (Figure 2).

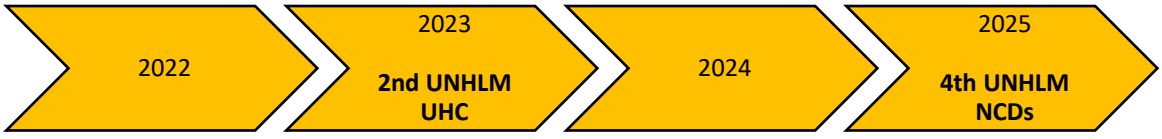



*Figure 2 - Timeline of key events for CAH advocacy and action*

@MATES4Kids acknowledges the need for data, discourse and decisions (Figure 3) and the opportunities for the WHO UHC Compendium (World Health Organisation 2022b) to inform our efforts to achieve sustainable change.

## Data

This briefing paper has been prepared for WHO in an initial and rapid attempt to present the latest "data" relevant to CAH and equitable access to medicines and equipment for the entire Community. Whilst limited to peer-reviewed literature, publicly available case studies and grey literature from professional networks, the evidence on the need for change is still compelling. This paper enable all stakeholders to come together with a shared knowledge. We acknowledge more data are needed. We will continue to clarify gaps, and create, collate, analyse and share data to further inform evidence-based decisions and actions.

## Dialogue

As we progress to "dialogue", @MATES4Kids welcomes a broad range of stakeholders willing to contribute to practical solutions in a tangible way and engage in collaborative efforts for and with the global CAH Community. To date, expressions of interest have been sought and confirmed from a range of stakeholders (Table 1) and we continue to welcome new partners to the movement. We believe WHO has a particular role to play in facilitating the dialogue by helping us create a forum that stakeholders might be encouraged to attend, review the data, and agree decisions. For instance, we know Ministries of Health and regional WHO offices will have a key role to play. Representatives from the pharmaceutical industry will also play a key role and we thank those already actively engaged.

## Decisions

In coming together, and sharing data, stories, achievements and insights with one another, and prioritising the voices of CAH Communities most inequitably affected, we expect to identify some practical solutions and initiatives. These can be enacted, sustained and scaled with urgency, such that #EVERYchild diagnosed with CAH around the world might enjoy affordable and sustainable access to essential medicines and equipment. We seek to stem the preventable mortality currently associated with CAH by 30% by 2030. We want to leverage the successes of the Diabetes and Cancer Communities, and in turn, hope our own achievements might also translate to change for other childhood NCD Communities.

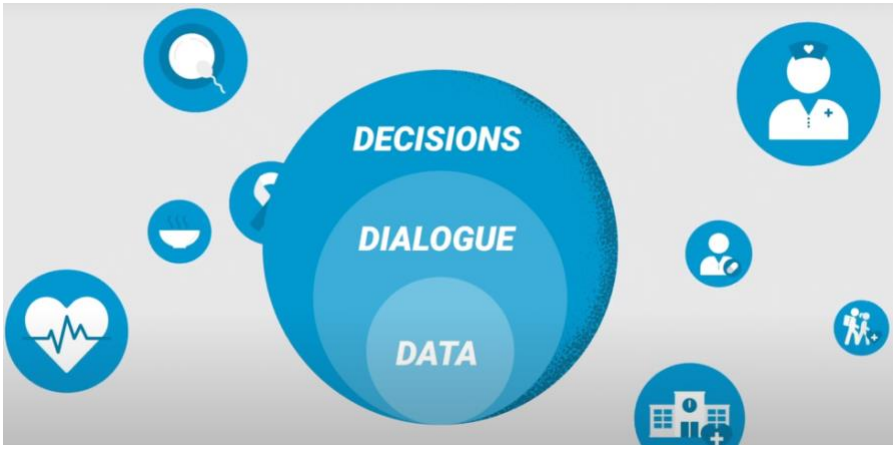



*Figure 3 - World Health Organisation's UHC Compendium Framework (World Health Organisation 2022b)*

| CAH Stakeholder | Organisation name (confirmed) |
|---|---|
| **CAH Communities** | CARES (USA) |
| | CLIP (Pakistan) |
| | IKAHAK & KAHAKI (Indonesia) |
| | CAHSAPI (Philippines) |
| | Nigerian CAH Community |
| | Zimbabwe CAH Community |
| | European CAH Communities |
| | CLAN Africa |
| **Health professionals** | APPES (Asia Pacific Pediatric Endocrinology Society) |
| | IPA (International Pediatric Association) |
| | PSPME (Philippines Society of Pediatric Metabolism & Endocrinology) |
| | IDAI (Indonesian Pediatric Society – Ikatan Dokter Anak Indonesia) |
| | Society of Paediatrics and Adolescents Endocrinology for Nigeria (SPAEN) |
| | SPED (Society Pediatric Endocrinology & Diabetes) |
| | APPA (Asia Pacific Pediatric Association) |
| **Other NGOs** | IndigenousNCDs |
| | NCD Child |
| | Life For A Child |
| | Cancer Warriors, the Philippines |
| | GiveAsia, the Philippines |
| | CLAN (Caring & Living As Neighbours) |
| | Global Pediatric Endocrinology and Diabetes (GPED) |
| **Academia** | Lehigh University (USA) |
| **Other** | TBC |
| **Pharmaceutical organisations** | Manufacturer of hydrocortisone and fludrocortisone tablets in Pakistan is currently collaborating with CLAN and health professionals in Zimbabwe to facilitate access. |

*Table 1 - Stakeholders currently committed to @MATES4Kids*

## Methods

This briefing paper has been prepared for WHO and other key stakeholders in an attempt to rapidly assess and collate the most up-to-date CAH evidence base, particularly relating to equitable, affordable access to essential CAH medicines and equipment. A rapid review of the literature (both peer-reviewed and grey literature sourced from publicly available material shared by established CAH Community groups and related ally organisations) has been augmented by case studies and success stories. Where appropriate, personal communication with recognised subject matter experts has been sought (and acknowledged).

# An introduction to CAH

## What is CAH?

Congenital adrenal hyperplasia (CAH) is the most common adrenal disease of childhood, and one of the more common inheritable disorders (Wu et al. 2011). CAH is an autosomal recessive condition, and in over 95% of cases is caused be a deficiency in the 21-hydroxylase (CYP21A2) enzyme (Merke & Auchus 2021).

### Adrenal hormone production and control without CAH

An adrenal gland sits above each kidney. In children and adults without CAH, the 21-hydroxylase enzyme is produced in and acts on the adrenal glands, where it affects the production of three main hormones: cortisol, aldosterone and androgens. Hormone production by the adrenal glands is controlled by the pituitary gland (in the brain), which releases an adrenal stimulating hormone into the blood when it detects low levels of cortisol in the circulating blood stream (Figure 4), thereby triggering the adrenal glands to produce more cortisol.


*Figure 4 - Feedback loop controlling the adrenal gland*

This hormone feedback loop achieves close control of the production of cortisol, aldosterone (salt-retaining hormone) and androgen (Figure 5). Androgens are hormones responsible for male sex characteristics and are present in both males and females (albeit in smaller quantities in females).

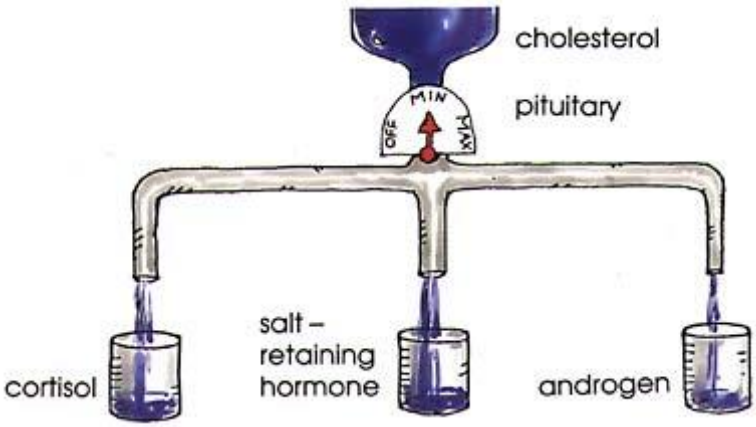



*Figure 5 - Pituitary feedback loop control of adrenal hormone production in people who do not have CAH*

Cortisol, also known as the 'stress hormone', is essential for life, acting on nervous, immune, cardiovascular, respiratory, reproductive and musculoskeletal systems (Thau et al. 2021). In doing so, cortisol serves many functions, including mediating humans' stress response, metabolism, inflammatory pathways and immune function.

Aldosterone predominantly acts in the kidney to regulate sodium reabsorption and potassium excretion. It also helps moderate blood pressure (Scott et al. 2021).

## Adrenal hormone production and control with CAH

In people who are living with CAH, 21-hydroxylase enzyme deficiency (21OHD) in the adrenal glands impedes the production of cortisol and aldosterone hormones. This causes accumulation of biochemical precursors which are instead utilised by the adrenal glands to make androgens, notably testosterone (Scott et al. 2021). The result is androgen excess (Figure 6).

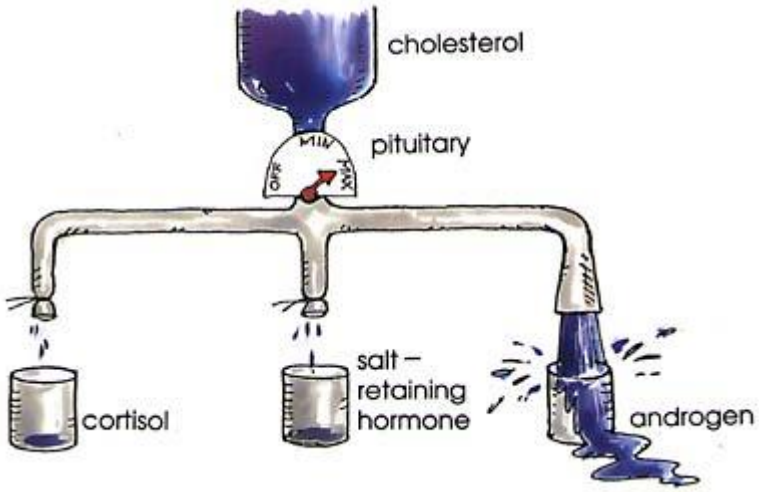



*Figure 6 - Androgen excess resulting from 21-Hydroxylase deficiency*

## How does CAH present?

In many high-income countries, routine heel-prick newborn screening (NBS) for CAH is mandatory, leading to early diagnosis and pre-emptive management (Merke & Auchus 2021).

In the absence of NBS, Classic CAH (21-hydroxylase enzyme deficiency) usually presents in two forms:

1) **Salt wasting (SW) CAH**: Of children with 21OHD, 75% of patients have the most severe, classic, 'salt-wasting' form of CAH, which is caused by a larger genetic defect and results in almost zero 21-OH enzyme activity and therefore total dependence on glucocorticoid and mineralocorticoid replacement medication several times a day for survival. Female infants are usually identified at birth because of ambiguous genitalia (caused by androgen excess in utero). While this experience is extremely traumatic for parents and families, girls with CAH are at least more likely to survive than their male counterparts because of this earlier diagnosis.

   Male infants with SWCAH generally present in the first twenty days of life with non-specific symptoms and signs including: failure to thrive, darkened skin, vomiting, diarrhoea, dehydration, lethargy, severe electrolyte disturbances and haemodynamic instability (Merke & Auchus 2021). These "Addisonian crisis" features occur as a result of cortisol deficiency, and are frequently misdiagnosed in resource poor settings. While the risk of infant death from adrenal crisis is approximately 4% in advanced hospital settings (Grosse & Van Vliet 2007), mortality rates are considerably higher in areas of poorer health access and literacy. This has resulted in the vast majority of people living with CAH in low- and middle-income countries being genetically female, despite the equal genetic predisposition between genders.

2) **Simple virilizing (SV) CAH**: The remaining 25% of children with 21-OHD present with a spectrum of enzyme deficiency, which results in impaired cortisol production and increased androgen production. SVCAH can be diagnosed early where NBS programs are universally available and similarly respond well to treatment. However, in LMICs, SVCAH usually presents later in childhood, with both males and females presenting with growth irregularities (usually tall at an early age, followed by short stature due to premature fusing of bony growth plates); premature puberty; menstrual irregularity in women; or in very mild cases, no symptoms at all (Merke & Auchus 2021).

Regardless of the type of enzyme deficiency, all young people and adults living with CAH that have been poorly managed during childhood are at increased risk of experiencing precocious puberty, virilisation, premature osteoporosis, cardiovascular disease and adult short stature (Merke 2021). Childhood presents a "golden window" during which optimal management of CAH determines future quality of life.

## Burden of CAH

### Incidence

Worldwide data are most usually informed by NBS programs and trials, and suggest an average CAH incidence rate of 1 in 15 000 live births (Merke & Auchus 2021).

**Did you know?**
Incidence rates of CAH vary internationally. Newborn screening programs reflect the most accurate incidence estimates. CAH affects:

- 1: 280 people in native Alaskan communities
- 1: 14,000 people in the Philippines
- 1: 20,000 people in Australia
- Unknown in Zimbabwe

However, the incidence of CAH varies remarkably between different ethnic groups and countries, with rates as low as 1 in 28 000 in Chinese populations (Li et al. 2021), and as high as 1 in 280 in native Alaskan peoples (Pang et al. 1982). Given the recessive nature of CAH, rates are generally higher in countries where consanguinity is more common.

While a carrier rate of 9.5% has been observed in middle European population (Baumgartner-Parzer et al. 2005), there is little comprehensive data on global carrier prevalence. Another study estimates that 2-7.5% of people carry the genes for CAH, with carrier rates varying between ethnicities (Hannah-Shmouni et al. 2017).

While more females than males are known to have CAH in LMICs, this does not reflect any genetic predisposition. Rather, as mentioned earlier, males and females are equally likely to be born with CAH genetic defects. However, girls are usually diagnosed and receive treatment earlier in LMICs simply because ambiguous genitalia is more obviously diagnosable than the more non-specific 'failure-to-thrive' symptoms of adrenal crisis seen in male infants with CAH at two to three weeks of age. Gender imbalances in CAH populations are therefore a marker of preventable mortality.

### Prevalence

The prevalence of CAH in different countries is not well established due to the absence of national registers and databases. In high-income countries with universal NBS programs in place and low preventable mortality, numbers can be estimated with some accuracy.

**Did you know?**
The prevalence of CAH in a country is most likely a reflection of mortality, not incidence.

At one paediatric hospital in Vietnam in 2005 it was estimated 150 children were alive with CAH. In 2018, after a decade of collaborative action for equity, the estimated prevalence of CAH at this same hospital had increased to 1235 children.

The profound shift reflected a broad range of successful strategic efforts to improve health outcomes for the CAH Community of Vietnam (Armstrong et al. 2020). Mortality improved, incidence did not increase!

In LMICs NBS is rarely available, treatment is unaffordable, quality of healthcare is poor, and the social stigma and shame associated with ambiguous genitalia is high. In the absence of NBS, diagnosis is routinely missed. Because of these factors, low prevalence of CAH in any country must be assumed to entirely reflect preventable mortality rather than low incidence until proven otherwise.

## Treatment of CAH

The mainstay of CAH treatment is pharmacological: twice or thrice daily glucocorticoid replacement therapy, alongside daily or twice daily mineralocorticoid replacement therapy in salt-wasting forms of CAH.

Glucocorticoids are typically administered as hydrocortisone (cortisol) orally three times a day at a dose of 12-15mg/$m^2$/day, with higher doses potentially needed in early infancy (Therapeutic Guidelines 2021). Limited data suggests other longer-acting glucocorticoids, such as dexamethasone, prednisone and prednisolone, may result in growth impairment in younger children and increase risk of Cushing syndrome (Merke 2021; Therapeutic Guidelines 2021). Because of these concerns, hydrocortisone is the standard medication of choice for CAH in early childhood.

Lifelong mineralocorticoid replacement with fludrocortisone is also required for CAH patients, with 50-200 micrograms administered once or twice daily orally (Therapeutic Guidelines 2021).

**Did you know?**
The most recent internationally endorsed CAH Treatment Guidelines were released by the Endocrine Society, a global community of 18,000 endocrine researchers and practitioners in 2018 (Abad et al. 2017).

The CAH Treatment Guidelines were cosponsored by: CARES Foundation, the European Society of Endocrinology, the European Society for Paediatric Endocrinology, Societies for Pediatric Urology and the Pediatric Endocrine Society.

The Therapeutic Guidelines are regularly reviewed and updated (most recently in 2021).

Ideally, children with CAH should be regularly monitored with growth charts, blood tests and bone mineral density imaging (Merke 2021). Three monthly follow-up during infancy can gradually be reduced over time, with annual specialist follow up in adulthood recommended.

Patients with CAH are at increased risk of adrenal crisis during acute illness, such as fever, vomiting or diarrhoea, and trauma or injury (Merke 2021). The symptoms of an adrenal crisis can initially be subtle, and include fatigue, nausea and vomiting, but patients can progress to loss of consciousness and haemodynamic instability. Because of a genetic inability to produce cortisol during acute illness or injury, individuals with CAH require 'stress-dosing' of hydrocortisone, and this can be administered orally (as a double or triple dose of hydrocortisone), or intramuscularly (IM) or intravenously (IV) in circumstances where oral intake is not tolerated. Because of the rapid onset of adrenal crisis, all CAH patients and families should have access to emergency IM hydrocortisone solutions with syringes and needles, and patients and their parents should be trained in recognising acute indications for injections and IM injecting technique. CAH patients are also strongly encouraged to wear medical alert identification to ensure appropriate treatment in emergencies where they may be unable to notify health professionals of their CAH for whatever reason.

Bilateral adrenalectomy can be occasionally considered in the management of CAH: those who have failed conservative, medical therapy, or developed iatrogenic Cushing syndrome or unresponsive hyperandrogenism (Merke 2021). This surgery lowers certain circulating hormone levels (adrenal androgen, progesterone, 17-hydroxyprogesterone), allowing for lower therapeutic doses of glucocorticoids and thereby reducing glucocorticoid adverse effects. Unfortunately, this also increases patients' reliance on glucocorticoid and mineralocorticoid medications, heightening the risk of adrenal crisis, especially where compliance with therapy is a challenge. Bilateral adrenalectomy therefore serves as a second line treatment option and would not be a preferred option in LMICs where access to medicines can be inconsistent.

Likewise, genitoplasty for females living with CAH who are born with ambiguous genitalia is another consideration. However, surgery can only be considered once access to medicines is secure, as virilisation will continue without medication to suppress excess adrenal androgen production.

Psychosocial support for young people living with CAH is important, and supportive school environments are essential to helping children survive and thrive.


*Figure 7 - Booklet in Bahasa Indonesia to support young women living with CAH (CLAN Child Health 2019b)*

Excellent educational resources are increasingly available for families and young people living with CAH. Resources in local languages, such as an innovative booklet for young women living with CAH in resource poor settings (Figure 7), are particularly powerful. Resources that support teachers to learn more about how to care for children with CAH in their classrooms (Figure 8) are also vitally important, accessible online and available for translation into other languages.


*Figure 8 - New video available to support teachers and caregivers on management of CAH in schools.*

## Prognosis

The prognosis associated with CAH is exclusively dependent on management. Outcomes seen in high-, middle- and low-income countries differ enormously.

**Did you know?**
Burundi is the poorest country in Africa and has a population of 12 million people. There are currently no people known to be living with CAH in Burundi.

Preventable mortality associated with CAH is directly associated with poverty and inequitable access to essential medicines and equipment.

With treatment and appropriate long-term management, patients with CAH have relatively normal life expectancy and high quality of life. Children with CAH have been shown to not report a lower quality of life than health comparatives in developed countries with good healthcare access (Halper et al. 2017).

## Mortality

Mortality rates can be mitigated globally through universal NBS, affordable access to medicines and quality healthcare, parental education, and clinician awareness. With strategic, collaborative action, rapid reductions in preventable mortality are achievable in low-income countries. Vietnam has witnessed a profound increase in prevalence of CAH in recent years, with a jump from **150** children at the National Children's Hospital in Hanoi in 2004 to **1235** cases in 2018, representing a **723%** increase over 14 years (Armstrong et al. 2006).

Even in countries where CAH medication is affordably available and newborn screening universal, the risk of mortality for babies born with CAH is threefold higher than unaffected children. This is because of the increased occurrence of routine infections in this age group which carry a subsequent risk of adrenal crisis (Merke 2021). Parents require support, education and access to the appropriate medication (hydrocortisone for injection) and equipment to optimally manage acute illness in their child with CAH.

## Morbidity

Adult patients with CAH can experience disease- and treatment-related complications, including growth impairment, subfertility, osteoporosis, and cardiovascular disease (Kamoun et al. 2013). Impaired growth is often a result of suboptimal treatment, especially during the critical periods of infancy and puberty. With proper medical treatment, patients with CAH can fulfil their genetic height potential. Similarly, on monitored glucocorticoid treatment where over-treatment is avoided, bone mineral density is generally preserved and osteoporosis avoided. There is increased obesity, hypertension, insulin resistance and dyslipidaemia in CAH patients. Second to adrenal crisis, cardiovascular disease is the most common cause of death (Merke 2021).

Subfertility in females can be attributed to androgen excess, complications of genital reconstructive surgery, secondary polycystic ovarian syndrome (PCOS) and psychological factors (Reisch et al. 2011). Recent studies show a significant increase in female fertility rates in high-income countries in recent years (Kamoun et al. 2013). This serves as further evidence for the improved outcomes that are possible with earlier treatment and compliance, and also reflects the advancements in reconstructive surgery. Subfertility in males is preponderantly caused by testicular adrenal rest tumours (TARTs) which are most usually seen where control of CAH is suboptimal. Early glucocorticoid initiation at increased doses may cause tumour regression and thereby reduce male subfertility, but this warrants further research (Claahsen-van der Grinten et al. 2009; Reisch et al. 2011).

### Quality of life

Merke (2021) and Reisch et al. (2011) found the most significant reduction in quality of life in adulthood was related to social factors such as negative body image, sexual inactivity, psychosexual identification, reduced self-confidence and social acceptance. Many factors may contribute to these experiences, including genital reconstruction surgical outcomes, growth impairment and obesity. These can be tackled with ever-improving surgical advancements; optimising treatment regimes, follow-up and monitoring to mitigate side effects; and improved patient and community awareness.

Overall, there are mixed findings as to the degree of impact CAH has on quality of life, which may be partially attributed to the differences in health care access and delivery. In a 2021 study, Verhees et al. (2021) evaluated the quality of life (QOL) in men living with CAH in six high-income European countries. They demonstrated that ‘disease severity and poor treatment control are inversely associated with quality of life’. Men who received treatment in keeping with international CAH guidelines scored comparably to healthy controls, and higher than patients with other chronic diseases and female patients with CAH. High reported quality of life in developed countries was supported by a systematic review performed by (Zainuddin et al. 2013). This positive prognosis is further incentive for optimising CAH management globally, as it results in high quality-adjusted life years, which cannot be said for all non-communicable diseases. It also promotes increased intervention for the complications experienced by females with CAH.

There exists limited data on the quality of life of patients living with CAH in low- and middle-income countries. An Asia-based study by Zainuddin et al. (2013) identified numerous additional obstacles to maximising quality of life in developing countries (Figure 9). These included delayed diagnosis, due to both lack of screening and resource-poor healthcare systems, leading to ‘gender assignment’ incongruent with a child’s genotype. For example, in one Pakistani hospital over 30% of females were initially assigned as male, which can have social, emotional and psychosexual consequences. This is supported by an Indian study that found 25% of patients were misgendered, which involved removal of female genitalia and insertion of testicular prosthesis (Bhansali et al. 2009). This management was significantly influenced by parental pressure and patriarchal Indian culture, and also resulted in social and emotional complications, alongside infertility. In addition, Seneviratne et al. (2021) found increased prevalence of gender dysphoria in girls with CAH in Asia, and attributed this predominantly to prenatal androgen exposure. This offers another

complexity to medical and psychological management in girls with CAH because culture and religion play major roles in the effect of disorders of sex development and gender, such as CAH, on quality of life (Warne 2008). However, few studies have been performed in Asia and Africa on this topic, and so further research is warranted.

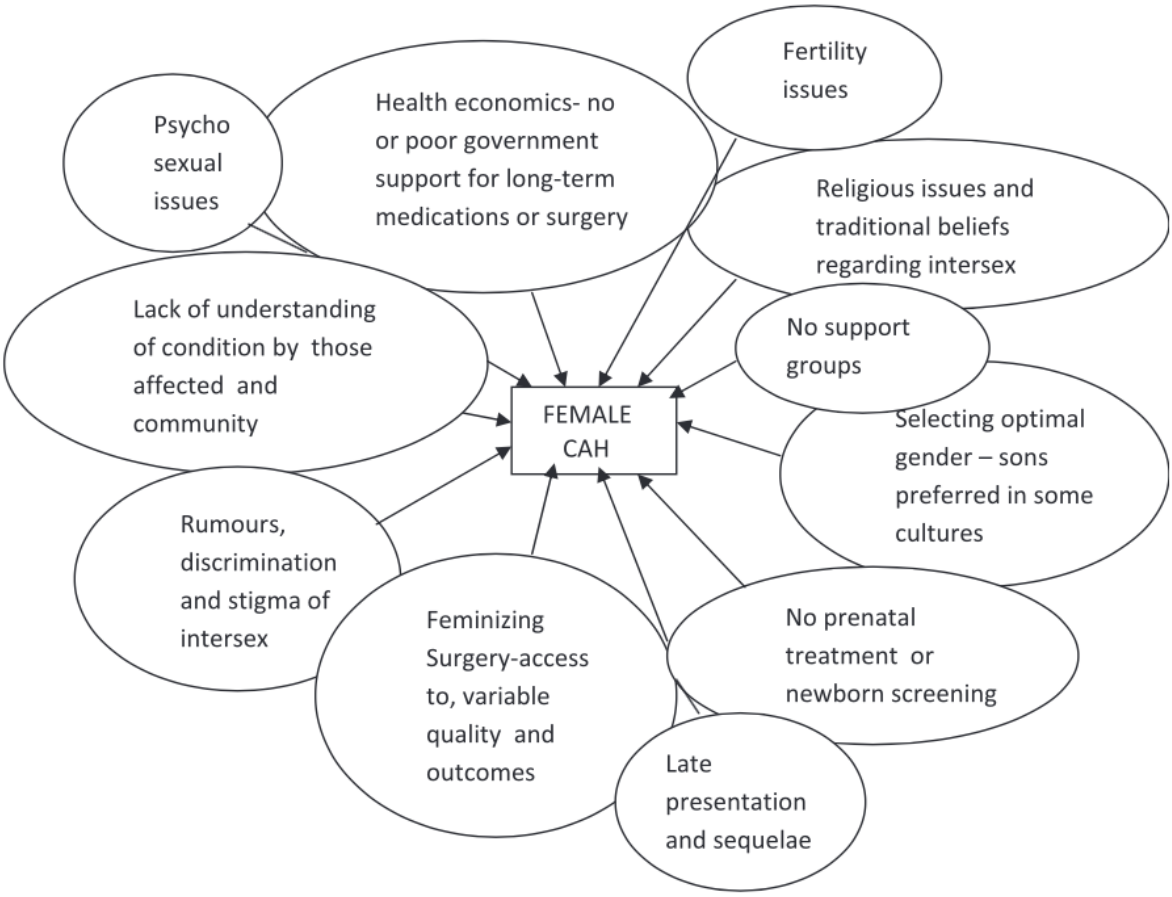



*Figure 9 - Issues faced by female CAH patients in developing countries (Zainuddin et al 2013)*

In Brazil, Gilban et al. (2014) studied quality of life in children and adolescents with CAH through self-reporting and parent-reporting methods. They showed a significant reduction in quality of life in physical, and social and emotional dimensions, compared to healthy controls. Parents were also demonstrated to experience notable psychological distress. The reduced quality of life associated with CAH was predominantly linked to poorer psychosocial management rather than clinical severity of disease. This is reaffirmed by Daniel et al. (2021), who found that fatigue and quality of life was significantly worse in parents of children with CAH than healthy controls. Gilban et al. (2014) therefore emphasise the importance of community and psychological support in optimising quality of life in CAH patients and their families. For example, Daniel et al. (2021) suggest routine assessment of perceived quality of life in children living with CAH and their parents to improve clinical care and reduce carer stress.

An Egyptian study by Musa et al. (2020) reaffirmed these findings. Using the WHO QOL-BREFF questionnaire, Musa et al. (2020) identified age, poor hormonal control, frequent

hospitalisation, and medical complications as factors associated with worse quality of life in CAH patients. Males demonstrated lower scores in the physical domain, which included infertility, hypertension, hirsutism, and frequent hospital admissions. Females scored lower in the psychological domains, which were related to age and timing of genital surgery.

In Vietnam, Armstrong et al. (2006) found quality of life of CAH patients and their families was compromised by the inaccessibility and high cost of medicines, limited awareness, and lack of access to resources and support groups.

# Access to medicines and equipment for the global CAH Community

## Rationale for a focus on access to medicines and equipment for NCDs

### A rights-based approach

The United Nations Convention on the Rights of the Child (UNCRC) (United Nations 1990) makes it clear that every child has the right to live an individual life in society and be brought up in the spirit of happiness, love, understanding, peace, dignity, tolerance, freedom, equality and solidarity. We all have a role to play in protecting and promoting the rights of children to life and health and ensuring children and young people living with CAH understand their rights under the UNCRC.

Educational resources, such as these Child-friendly Rights Flyers available online (CLAN Child Health 2019a), can help to raise awareness and empower children, families, communities and allies ( Figure 10). Information is power and can guide advocacy efforts. Articles 6, 23 and 24 in the UNCRC clearly support affordable access to essential medicines and equipment for children living with CAH and other NCDs (Figure 11), and yet too often action to drive change is seen as an act of charity rather than one of justice.

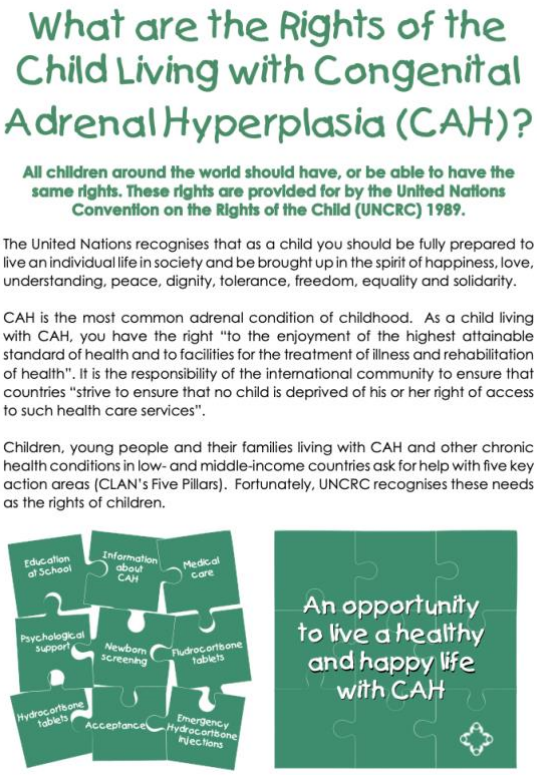



*Figure 10 - Child-Friend CAH Rights Flyer*


*Figure 11 - The rights of the child to affordable access to medicines and equipment as outlined in the United Nations Convention on the Rights of the Child (UNCRC)*

## A global commitment to action on NCDs

The UN Sustainable Development Goals (and specifically, SDG 3.4) demand a 30% reduction in preventable mortality from non-communicable diseases (Figure 12). This right to health and life is reaffirmed by the WHO Global NCD Action Plan (2013-2020) (World Health Organisation 2013), which commits to 'support national efforts' to spread awareness and actively combat NCDs, which are the world's number one cause of death.


*Figure 12 - SDG 3.4 (United Nations Department of Economic and Social Affairs 2021)*

While existing indicators strictly limit attention to people aged 30-70 years, the United Nations Convention on the Rights of the Child (UNCRC) speaks to the responsibility we all share to promote and protect the rights of children to life and health. The inequity of diagnosis and treatment of NCDs between high- and low-income countries means that LMICs experience 86% of NCD-related premature deaths. This results in millions of people perpetually trapped in poverty due to cumulative economic losses of $US7 trillion in the fifteen years after premature death. Therefore, the flowing ramifications from NCD inequity perpetuate global social and economic inequality and demand further action from leading bodies such as WHO.

With so much action to reduce the preventable mortality associated with NCDs, there is an opportunity to learn from others and avoid re-inventing the wheel. WHO and other groups can draw from existing NCD work, especially in the fields of diabetes and cancer for which there already exists data, collaboration, supply chains, and strong partnerships.

## Rationale for a focus on access to medicines and equipment for CAH

### Inequitable health outcomes

CAH is increasingly recognised as contributing to the global NCD burden facing children under the age of five (Bukhman et al. 2020) and is an NCD with immense scope for improved outcomes in low- and middle-income countries. The massive inequity between resource rich and poor countries in CAH-related morbidity and mortality speaks to the potential for change when effort and resources are directed to address preventable deaths and loss of quality of life. Strong indicators of this disparity include lower prevalence, unequal gender distribution (males being more likely to die from undiagnosed salt-wasting crises) and high mortality, which reflect inequitable healthcare access rather than low CAH incidence (Alfadhel et al. 2017; Armstrong et al. 2020).

### CAH medicines are already in the WHO EMLc

Inequitable access to essential medicines is an urgent priority. The WHO includes fludrocortisone and hydrocortisone on its Model List of Essential Medicines for Children (World Health Organisation 2021). Whilst the majority of high-income countries include hydrocortisone and fludrocortisone tablets in their National Essential Medicines Lists (NEML), many LMICs' NEMLs do not include these life-saving medicines. Some examples include Somalia, Afghanistan, Yemen, Syria and Djibouti (Rowlands et al. 2021). In too many cases, even when countries include the medicines in their NEML, it does not guarantee affordable access for all. Addressing the discrepancies in national NEMLs is a valuable target given the positive correlation between inclusion of fludrocortisone and hydrocortisone in NEMLs and the potential for inclusion within Universal Health Coverage processes within that country.

**Case Study – Inclusion of hydrocortisone and fludrocortisone within the WHO EMLc**

In 2008 the international CAH Community united to submit an application to the WHO for the inclusion of hydrocortisone and fludrocortisone tablets in the WHO Essential Medicines List for Children (EMLc). The application was approved, and this has greatly assisted subsequent advocacy efforts to improve access to both drugs in different countries.

There is still more work to be done. Inclusion of drugs in the WHO EMLc is not a panacea. Many countries have still not included hydrocortisone or fludrocortisone in their National EMLs. Likewise, the WHO Essential Diagnostics List (EDL) does not yet include 17OHP testing, which plays a vital role in the diagnosis and management of CAH.

## The importance of essential medical equipment and diagnostics

Alongside the WHO EML, since 2018 WHO has published an Essential Diagnostics List (EDL) (World Health Organisation 2020), with the Third EDL published in January 2021. WHO is working towards National EDL introduction. To date there is no mention of 17OHP or androstenedione in the WHO EDL, either of which must be used to make a diagnosis of CAH (the latter being preferred in developed countries, but being a more specialised test is less accessible in many LMICs). Hormonal diagnosis and monitoring play an essential role in CAH, comparable to blood glucose and HbA1c in diabetes. These investigations are vital to diagnose and monitor CAH, and therefore should be considered as equally essential as the treating medicines. Moving forward, aligning WHO's EDL with the EML would be rational and bolster diagnosis of CAH globally.

## Newborn screening has the potential to save many lives

Inclusion of NBS in the WHO EDL could be another consideration. There is unequal access to NBS internationally, with LMICs particularly disadvantaged, despite the clear evidence demonstrating the effectiveness of NBS in reducing morbidity and mortality (Costa de Miranda et al. 2021; White 2009). Although there are clear challenges to setting up NBS in resource poor settings, some LMICs have championed NBS, proving it to be achievable (see case study below).

**Case Study – NBS for CAH in the Philippines (Padilla et al. 2021)**

The Philippines is an excellent example of a lower-middle income country excelling in the implementation of NBS. NBS started in the Philippines in 1996 and includes seven conditions in the panel: Congenital Hypothyroidism (CH), Congenital Adrenal Hyperplasia (CAH), Phenylketonuria (PKU), Galactosemia (GAL), Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency and Maple Syrup Urine Disease (MSUD), with haemoglobinopathies added more recently. Approximately 90% of all babies are currently screened and it is projected to reach every newborn child in the Philippines by 2030.

CAHSAPI is the CAH Community of the Philippines. It was founded in 2005 and continues to support families across the archipelago and has a strong membership on Facebook.

The major barriers to the establishment and implementation of NBS in resource poor settings are undoubtedly structural. Fractured health systems can limit the capacity of health professionals and systems to screen and contact families in a short period of time. Determination of screening panels is also complex. However, once established for one condition, the pre-existing framework makes it relatively simple to screen for additional conditions over time.

While other childhood NCDs are more commonly discussed and prioritised in the context of NBS panels (with Congenital Hypothyroidism an obvious and warranted example), there is no doubt the prevalence of CAH is greater in screened populations compared to unscreened

populations of similar ethnicities, showing that screening reduces mortality (Wu et al. 2011). Additionally, screening reduces late presentations with precocious puberty and short stature associated with SVCAH. According to Wu et al. (2011), a screening strategy for CAH is recommended because of the high morbidity and mortality if undiagnosed; the screening test is reliable (DELFIA method having >99% specificity and 92-100% sensitivity) and accessible; affordable treatment is available; and the incidence of CAH is relatively high. This is supported by The American College of Medical Genetics, which has deemed CAH as one of 29 conditions for which screening should be mandatory (Watson et al. 2006).

## CAH offers hope for other childhood NCD Communities

Achievements in the field of CAH have the potential to translate to other childhood NCDs and thereby further contribute to global efforts to reduce the preventable mortality associated with NCDs by 2030. Already we have seen the translation of CLAN's strategic framework for action from CAH to other childhood NCDs (such as asthma, Duchenne Muscular Dystrophy, epilepsy, nephrotic syndrome, osteogenesis imperfecta, type 1 diabetes and others) across a range of countries with tremendous impact. Likewise, the potential to expand newborn screening in LMICs is enormous.

The establishment of NCD Child (NCD Child 2022) in 2011 undoubtedly continues to strengthen the voices and participation of children and young people within the international NCD discourse, yet there is still an urgent need to bring too many childhood NCDs out of the shadows. A genuinely life-course approach to NCDs must move beyond a narrow interest in prevention of NCDs and instead consider the steps needed to achieve equitable access to treatment and optimal health outcomes for all people of all ages living with and at risk of NCDs.

## CAH Communities and voices are growing stronger

The international CAH Community continues to connect, care and share. The increasing presence of strong, active CAH communities, charities and NGOs provides avenues for change, and this muscle power can be harnessed by WHO and Member States. Some examples of such groups are listed in Figure 1.

Collaboration with WHO would benefit international CAH Communities enormously. The ability of grassroots groups to harness the power of WHO would facilitate efforts to:

a) Attract funding and resources
b) Advocate and raise awareness
c) Facilitate collaboration and communication between a broad range of stakeholders (including high and low/middle income countries, government and NGOs, patients and practitioners, manufacturers etc.)
d) Share insights and achievements to accelerate change
e) Create accountability through monitoring and critical evaluation.

## What do we already know about access to CAH medicine and equipment?

A rapid review of the publicly available evidence relating to access to CAH medicines and equipment indicates the following:

### Hydrocortisone & Fludrocortisone

A study by Rowlands et al. (2021) reviewed twenty-three countries in the Eastern Mediterranean Region (EMRO) for hydrocortisone and fludrocortisone availability. 57% of countries included fludrocortisone on their National Essential Medicine List (NEML), and 78% of countries included oral hydrocortisone. However, fludrocortisone was not included on the NEML in any low-income countries, and oral hydrocortisone was only included in one low-income country. Rowlands et al. (2021) noted a correlation between inclusion on the NEML and availability of these medications, indicating how exclusion from NEMLs are a current obstacle to hydrocortisone and fludrocortisone access in low-income countries.

Hydrocortisone has numerous uses for treatment of primary and secondary adrenal insufficiencies, of which there are many causes, meaning there are greater supplies (Rowlands et al. 2021). While hydrocortisone is preferred, it can also be substituted for prednisone or prednisolone, which are also manufactured in large quantities and used for many conditions. In contrast, fludrocortisone's use is limited to classic CAH and Addison's disease, so less is manufactured globally. This results in limited access in low- and middle-income countries. For example, Algeria does not produce fludrocortisone locally. It is imported in bulk semi-annually from Spain by select, compassionate healthcare workers, or imported directly by family abroad. Similarly in Morocco, fludrocortisone is never officially available on the market, and CAH patients either depend on family imports from abroad, or substitution of fludrocortisone with higher doses of hydrocortisone. The former is expensive and renders insufficient and unpredictable supply, while the latter causes greater adverse effects and poorer health outcomes. Even where there is local production of both medications, such as in Egypt, fludrocortisone is only available 50% of the time and only through private pharmacies.

Rowlands et al. (2021) make several recommendations to overcome the aforementioned obstacles to inequitable medicine supply and access:

1) Prequalification of hydrocortisone and fludrocortisone medicines by WHO
2) A common registration process that can be enlisted by a group of countries akin to European Medicines Agency
3) Pooled procurement such as that used by the Pan American Health Organisation
4) Use of local pharmaceutical companies, which accelerates national registration processes and is more sustainable
5) Special access schemes for medicines that are not registered in countries
6) Import or manufacturing of compounded capsules or oral suspensions, which can be purchased in bulk and are less expensive (however have a shorter half-life)

**Case Study – Pakistan achieves local production of CAH essential medicines**

Pakistan is a prime example of how inequalities in hydrocortisone and fludrocortisone access can be addressed (Rowlands et al. 2021).

In 2007 doctors in Pakistan requested support from CLAN to improve access to CAH medicines. A multi-year humanitarian donation of hydrocortisone and fludrocortisone tablets was secured to keep children alive while local efforts focused on achieving longer-term, sustainable solutions. While oral hydrocortisone and fludrocortisone were included in the 2018 NEML, they were not available to patients until 2020.

Led by a team of compassionate health professionals, and after years of collaboration with local and global supply chains and manufacturers, Pakistan now boasts local manufacturing of hydrocortisone. It has subsequently become available freely at hospital pharmacies, and cheaply in the community (US$0.02/10mg). In Pakistan, fludrocortisone is currently available >75% of the time.

With affordable access to both medicines now secured for citizens across Pakistan, local manufacturers are well placed to support CAH Communities in other countries. Specialist health professionals and the CAH Community of Zimbabwe are currently negotiating access for children living CAH in Zimbabwe with manufacturers in Pakistan. If appropriate systems and processes can be secured, children and families in both countries will benefit from the prolonged efforts of so many in Pakistan, and negotiations could then progress for other countries in Africa also.


### Hydrocortisone for Injection

Injectable hydrocortisone is more likely available in a hospital setting, given it is indicated in emergency salt-wasting crises, requires syringes and needles, and has other uses in a hospital setting. Rowlands et al. (2021) found across the EMRO, when injectable hydrocortisone is included on the NEML, it is available ~75% of the time within hospitals. However, this does not account for household injectable hydrocortisone and the associated equipment, which is equally less accessible in low- and middle-income countries due to the same barriers faced by oral hydrocortisone and fludrocortisone. Additionally, as with oral hydrocortisone and fludrocortisone, injectable hydrocortisone unavailability of 25%, especially in an unpredictable manner, continues to compromise patient care.

### Newborn Screening (NBS) for CAH

Newborn screening is not routinely available or performed in low- and middle-income countries, resulting in delayed diagnosis and increased morbidity and mortality (Rowlands et al. 2021). In these countries, the greater prevalence of CAH in females than males reflects the underdiagnosis and subsequent premature mortality in male patients with CAH (Musa et al. 2020; Rowlands et al. 2021). In the EMRO, where consanguinity and birth rates are especially high, NBS for this genetically recessive condition would be particularly impactful. Using the most conservative incidence estimates in this region, introduction of NBS would diagnose 2170 children every year.

In Maghreb countries (north-west Africa), Ladjouze et al. (2018) also recommend 'urgent' introduction of NBS for CAH because of the increased risk of developmental delay and mortality secondary to delayed diagnosis, and because of the increased prevalence of CAH due to consanguinity. Alshabab et al. (2015) similarly recommend introduction of NBS in Syria due to poor medical and public awareness, delayed diagnosis, and relatively high prevalence.

Unfortunately, the cost and logistics of introducing such a NBS program are challenges in LMICs. However, in countries where there already exists NBS for other conditions, such as congenital hypothyroidism, CAH screening could be more easily and affordably introduced. Similarly, given the main obstacle to NBS is the healthcare structures surrounding its initial implementation, once NBS is executed in LMIC there is enormous potential to expand its use to numerous NCDs beyond CAH.

### Diagnostic and monitoring investigations and resources

In addition to population-wide NBS screening, key tests for diagnosing and monitoring CAH in individual patients include: venous testing for 17-Hydroxyprogesterone (17-OHP), ACTH stimulation, renin, testosterone, aldosterone and androstenedione levels at different stages in the diagnosis and management of CAH. The majority of these tests are commonly unavailable in LMICs, such as in Zimbabwe where Harare-based paediatric endocrinologist

Dr Prisca Matyanga-Mureriwa describes these tests as ‘unavailable locally, and most samples are sent to South Africa, same with karyotyping’.

Growth charts are another important tool used in the routine management of CAH, with regular height and weight measurements throughout childhood giving an affordable and accurate indication of appropriate dosing and treatment. Health professionals benefit from training and education on the use of these affordable and readily available tools (World Health Organisation 2022a) and the importance of ensuring they are routinely used.

## Equipment challenges

In addition to the diagnostic, monitoring and newborn screening equipment referred to above, affordable access to other essential equipment can also pose challenges for children and families living with CAH in resource poor settings.

Some fludrocortisone manufacturers require cold chain logistics and storage at 4°C (Rowlands et al. 2021). Selection of a fludrocortisone brand that does not require refrigeration is therefore recommended.

Genetic analysis can be useful for differential diagnosis of CAH and fine-tuning of management and is unaffordable in most LMICs.

Access to needles and syringes by families for emergency management of adrenal crisis outside of the hospital is also ideal.

**Case Study – Sick day management of CAH: the need for syringes and needles**

Routine maintenance management of CAH is achieved with oral medications (hydrocortisone and fludrocortisone tablets taken several times a day). However, during acute illness and times of stress or injury, people living with CAH are not able to produce stress doses of cortisol to cope and are at risk of adrenal crisis. Oral replacement with hydrocortisone tablets in these situations is usually not sufficient (especially where there is vomiting and diarrhoea) and therefore access to intramuscular or intravenous cortisol is life-saving.

In high-income countries, it is routine practice for every family of a child with CAH to have access to a sick day kit in their own home. The kits contain hydrocortisone vials, needles and syringes and instructions on how to use in an emergency. Families are also taught how to give the injections during an adrenal crisis. Young people living with CAH learn how to self-inject as they grow older (much as people living with Diabetes learn how to self-inject with insulin).

Unfortunately, for families in most low and low-middle income countries, injection kits are not routinely available and the time taken to travel to a secondary or tertiary level health centre during an adrenal crisis can be too long. Tragically, in 2021 the CAH Community of Zimbabwe lost a member to an adrenal crisis for this very reason.

Children living with CAH in resource-poor settings are dying unnecessarily, from adrenal crises triggered by simple childhood infections and injuries that cannot be managed appropriately due to inequities of access.

## Other Barriers

A holistic approach to access is essential, and the wrap-around systems and structures necessary to improve access will be imperative if we hope to reduce preventable mortality associated with CAH. Whilst @MATES4Kids seeks to focus collaborative efforts on optimising affordable access to medicines and equipment, we also acknowledge consideration of the five dimensions of accessibility (approachability; acceptability; availability and accommodation; affordability and appropriateness) (Levesque et al. 2013) highlights the many barriers that can impact adversely on the capacity of children and families to access to medicines, equipment and healthcare more generally (Figure 13).

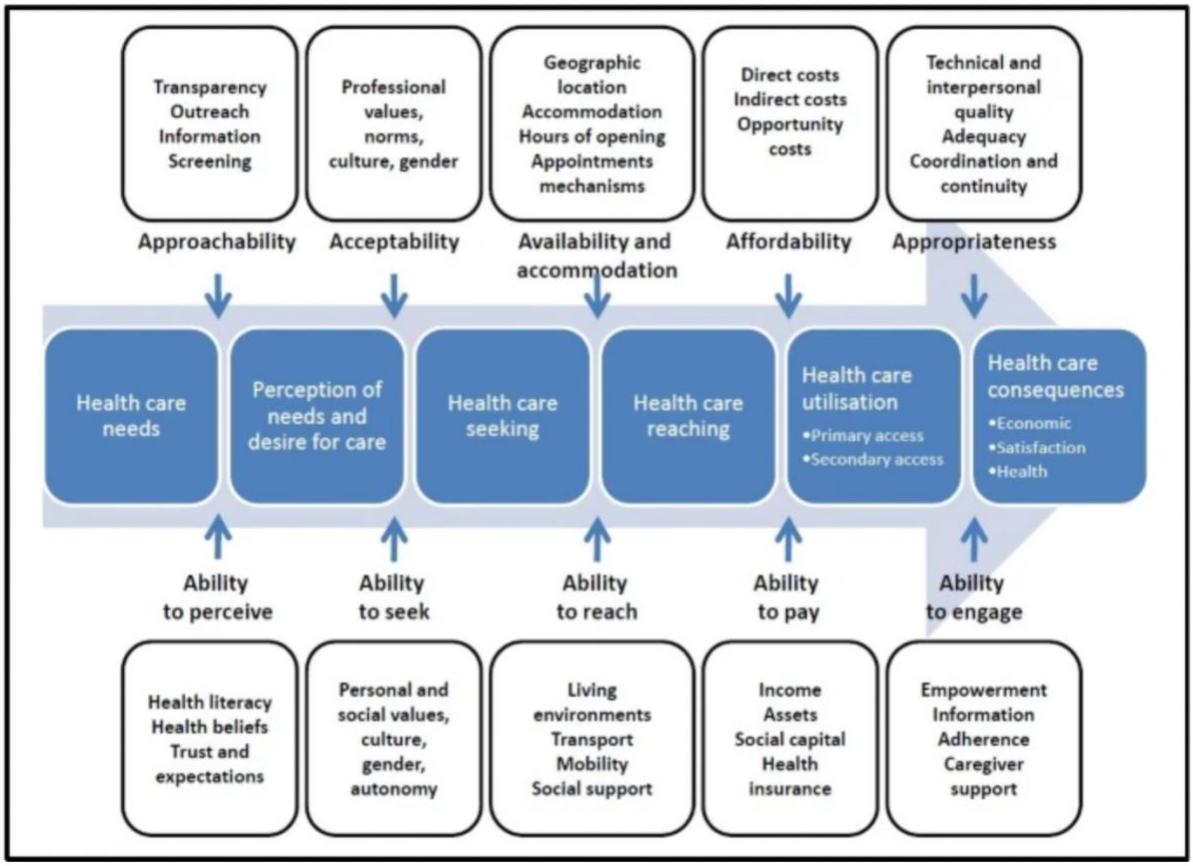



*Figure 13 - Conceptual framework of access to health care (Levesque et al, 2013)*

## Education and Training

Limited availability of educational resources increases the risk of hospitalisation, morbidity and mortality for people living with CAH and other NCDs. Access to resources in local language supports optimal management of CAH at all levels, and lack of accurate information fosters the development of myths and misinformation. Many communities in resource poor settings have limited access to reliable, accurate and translated information. For example, in Algeria, there exists only Arabic translations of publications from the European Society for Paediatric Endocrinology (Rowlands et al. 2021). In Egypt and

Palestine, no educational material is readily available or published regarding CAH for patients and their families.

National training programs for paediatric endocrinology are not yet available in many low and middle-income countries, and indeed, many countries do not have dedicated paediatric endocrinologists. Support is needed to build these professional networks regionally and nationally. Supportive health professionals are key to achieving national change for CAH Communities, and the establishment of specialist professional networks (such as the Society of Pediatrics and Diabetes (SPED), founded in Pakistan in 2015) are usually a good indicator of strong progress that will ultimately benefit children and families.

Likewise, CAH nurse specialists can play a vital role in supporting families and young people living with CAH. Again, training and opportunities for this level of specialist training are rarely available without specific interventions.

### Surgical Care & Other Resources

Specialist training in the management of ambiguous genitalia for girls born with CAH is largely unavailable, and children risk preventable trauma and morbidity. Wait times for genitoplasty are an issue given the prioritising of life-threatening surgeries, such as in Zimbabwe (Dr Prisca Matyanga-Mureriwa, paediatric endocrinologist in Harare). This is likely a reflection of under-resourced and under-staffed hospital systems.

On a related note, psychological support for families and young people living with CAH are not routinely available in LMICs, yet can play a vital role in promoting health and well-being. The cultural stigma and social isolation associated with CAH can be particularly extreme for young women.

### Conflict & Political Instability

Conflict poses an obvious barrier to medicine local production and access, such as that seen in Libya where access to hydrocortisone and fludrocortisone is variable (Rowlands et al. 2021).

### Poverty

The importance of the social and cultural determinants of health are well recognised. The aforementioned challenges are compounded by limited access to affordable medicine; reliance on private pharmacies, family imports and the black market for over-priced medication; limited education and access to culturally safe informational resources; and disruptions to employment as parents present with increasing frequency to hospitals and health professionals with their deteriorating child, further straining limited family budgets and emotional reserves.

Over time, poverty fosters a vicious cycle of morbidity and mortality, with financial distress ultimately a huge barrier even to those families who began the journey in a financially secure state. For example, in Vietnam, Armstrong et al. (2006) found poverty to be not just an obstacle to accessing medical care, but also a consequence for families living with CAH. This was due to the high cost of fludrocortisone and hydrocortisone on the black market, and the need to travel great distances to access specialist medical care in tertiary centres. Similar findings were reported in Malaysia, where high costs of travel and medicine, as well as parents having to miss work, were parental concerns (Zainuddin et al. 2013).

Innovative solutions that help families escape poverty by reducing expenditures and increasing income generation must be considered.

## The need to prioritise children living in the most vulnerable circumstances

An almost unending array of challenges inequitably burden children and families living in the most vulnerable circumstances. The COVID-19 Pandemic has been a powerful reminder of this. An innovative project led by health professionals at the National Institute of Child Health in Karachi, Pakistan, demonstrated the power of targeted action in protecting children at greatest risk of preventable mortality and morbidity associated with CAH (see Case Study below).

Other factors, such as climate change, racism, family breakdown, parental education levels and distance from quality health care (as experienced by families living in remote and rural settings) can also contribute to adverse health outcomes for children and young people living with CAH. Children living in the most vulnerable circumstances must be prioritised for innovative action that redresses inequities. A novel Child Health Equity Check Count (CHECC) scorecard has been developed to enable health professionals to rapidly identify children who are most at risk of not surviving the diagnosis of a chronic health condition, and CLAN is now working with partners to pilot the tool and ensure limited resources are targeted to achieve optimal health outcomes for all (Armstrong 2021).

**Case Study – CAH medicines to the doorstep of children living with CAH in the most vulnerable circumstances in Pakistan**

In 2019 CLAN awarded a grant of AUD $5000 to NICH (the National Institute of Child Health) in Pakistan, to benefit CLIP (CAH Living In Pakistan), the CAH Community based in Karachi. Local priorities identified the need for a project that would deliver essential CAH medicines from the hospital to the doorsteps of the most vulnerable families living in the most remote regions.

By chance, the project operated during some of the most challenging times of the COVID Pandemic and had remarkable results. Not one child died during the project, and all returned for routine medical checks which revealed good health outcomes. Specific efforts that benefit children living in the most vulnerable circumstances should be prioritised in every country.

## What change does @MATES4Kids seek?

**@MATES4Kids seeks equitable and affordable access to essential medicines and equipment for the global CAH Community. We believe achieving this will help us reduce preventable mortality associated with CAH by 30% by 2030.**

Currently, preventable morbidity and mortality associated with CAH in resource-poor countries is unacceptably inequitable (Armstrong et al. 2006; New 2006; Zainuddin et al. 2013). National snapshot surveys conducted by CLAN and partners in LMICs clearly demonstrate that the preventable and inequitable morbidity and mortality currently associated with CAH around the world is extreme.

If we are to reduce preventable mortality associated with NCDs for ALL people by 30% by 2030, we must find realistic, sustainable and scalable solutions to the challenges associated with affordable access to essential medicines for children and young people. Achievements to date in the Asia Pacific region (Armstrong et al. 2020) suggest change is possible when we all work together. Only in this way can we hope to truly leave no one behind.

The UN High Level Meeting on Universal Health Coverage (UNHLM on UHC) in 2023 and UNHLM on NCDs in 2025 offer key moments in time to track change and report on collective achievements with and for the global CAH community. @MATES4Kids propose ongoing collective efforts to collate data, promote discourse, identify decisions and recommendations that will have the greatest impact, and drive sustainable change for all.

Success will require active involvement of people living with CAH, and the CAH Community stands ready, willing and able to actively contribute and make a change. In the words of one CAH Community representative from a low-income country:

*"Of course we are very much interested even more now than before.*
*Yes, hydrocortisone is available but so exorbitant, parents are paying and sometimes exhausting their finances to maintain their child in control.*
*Yes, we can do more investigations but at a heavy cost too.*
*Yes, we can source reagent for stimulation test when necessary but also at a high cost.*
*The patients still reminiscent about when you gave us some hydrocortisone and wishes for that period in time."*

## Underlying Principles

Underlying principles guiding collaborative action for the global CAH Community and @MATES4Kids include (Armstrong et al. 2020):

- **A holistic view of health**—@MATES4Kids acknowledges the WHO definition of health (World Health Organisation Adopted by the International Health Conference in New York, USA on 22 July 1946, and came into Force on 7 April 1948), with a focus on body, mind and spirit, and an appreciation of the impact the socio-cultural determinants of health (SCDOH) (Marmot 2005) have on health outcomes.

- **Human rights-based approach**—Acknowledging rights and responsibilities as outlined in the United Nations' Convention on the Rights of the Child (United Nations 1990).

- **Equity**—Commitment to strive for excellence for all and respect, promote and protect the rights of children in high- and low-income countries to the highest quality of life possible.

- **Community development**—All children living with the same chronic health condition in a country are members of a community; these NCD Communities are considered interconnected and united at the local, regional, national and international level.

- **Community control**—People living with chronic conditions are experts and must be consulted at all stages when decisions are made around appropriate approaches and actions to drive change.

- **Person- and family-centred care**—Acknowledges the pivotal role children, young people and families play in all activities. Indeed, parents of children with chronic health conditions frequently commit to long-term action and advocacy to benefit not only their own children, but others with the same condition, and work tirelessly with caring health professionals and other stakeholders to facilitate real change.

- **Sustainable, ethical and transparent approaches to project management**—Commitment to the highest standards of accountability and reporting required of NGOs (by ACFID – the Australian Council for International Development) in Australia and to the United Nations (through GNEC and ECOSOC). @MATES4Kids is committed to sustainable approaches and responsible action in the face of climate change.

- **Multisectoral collaboration and partnerships**— Key to sustainability and success.

- **Above all do no harm**—Overarching guiding principle and informs all actions.

## Underlying Frameworks

The following three frameworks will inform the approach of @MATES4Kids:

### 1) CLAN's Strategic Framework for Action (Figure 14)

CLAN's strategic framework for action promotes a rights-based approach, focusing on a community of children living with a particular NCD as the visual hub of all collaborative action. This approach builds engagement between a broad range of multisectoral stakeholders and facilitates collective strategic action focused on five key pillars:

1) Affordable access to medicines and equipment
2) Education, research and advocacy
3) Optimisation of medical management
4) Encouragement of family support groups
5) Reducing financial burdens and promoting financial independence

@MATES4Kids seeks to specifically focus collaborative efforts on pillar one for the global CAH Community: affordable access to essential CAH medicine and equipment.

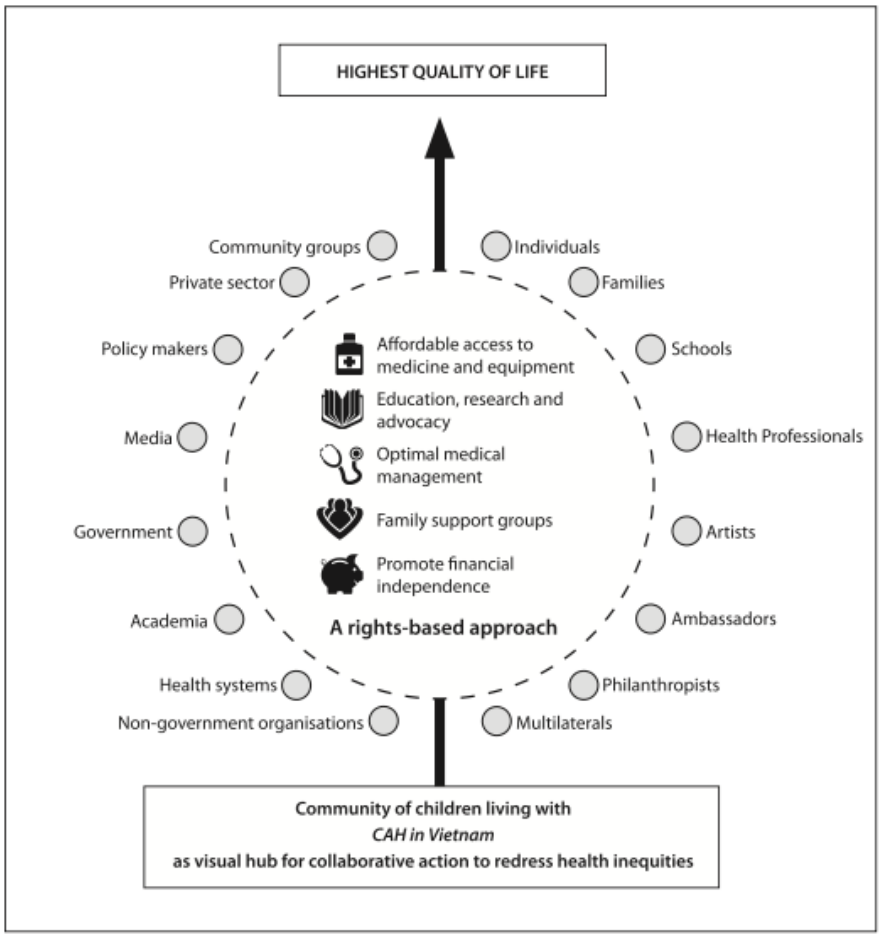
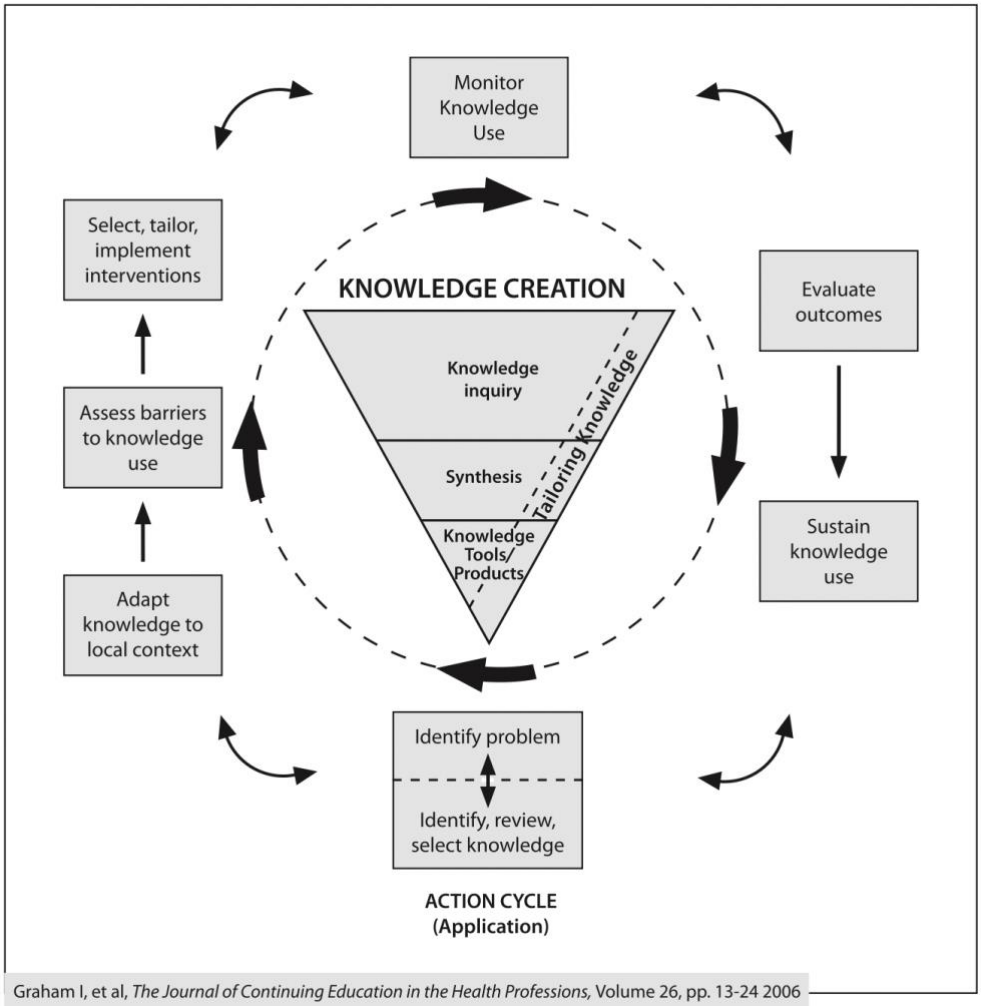



*Figure 14 - CLAN's Strategic Framework for Action - prioritising CAH Communities as a visual hub for collaborative action to redress inequities (Armstrong et al, 2020)*

### 2) Knowledge to Action Framework (Figure 15)

The Knowledge to Action (KTA) Framework (Graham et al. 2006) promotes an evidence-based, continuous quality improvement approach to improving health outcomes, with efforts adapted locally to ensure optimal impact of priority interventions. Knowledge, tools and resources are refined over time, thereby facilitating sustainable and scalable action to address specific problems. The KTA Framework and CLAN's Strategic Framework for Action have been demonstrated effective tools for driving national change for children living with NCDs (Armstrong 2021).

@MATES4Kids commits to bringing key stakeholders together to clearly articulate the key challenges facing the global CAH Community with regards to affordable access to essential medicines and equipment. Additionally, @MATES4Kids aims to provide opportunities for genuine collaborative action and implementation of select interventions that will affect real, sustained and scalable change. Innovative approaches, insights, resources and tools will then be available to other childhood NCD Communities.




Graham I, et al, *The Journal of Continuing Education in the Health Professions,* Volume 26, pp. 13-24 2006

*Figure 15 - Knowledge To Action Framework (Graham et al 2006)*

### 3) Ottawa Charter and the five priority actions (Figure 16)

The Ottawa Charter identifies five key priorities for action:

1) Create supportive environments
2) Develop personal skills
3) Reorient health systems
4) Strengthen community action
5) Build health public policy

It also acknowledges the imperative to:

- Enable
- Mediate
- Advocate.

In doing so, the Ottawa Charter aims to promote health and well-being.

@MATES4Kids seeks sustainable change. We commit to the advocacy and action needed to achieve this. We acknowledge the imperative of involving powerful organisations and stakeholders if we are to change public policy, transform health systems, strengthen community action, and create the supportive environments needed to reduce preventable mortality associated with CAH by 30% by 2030.

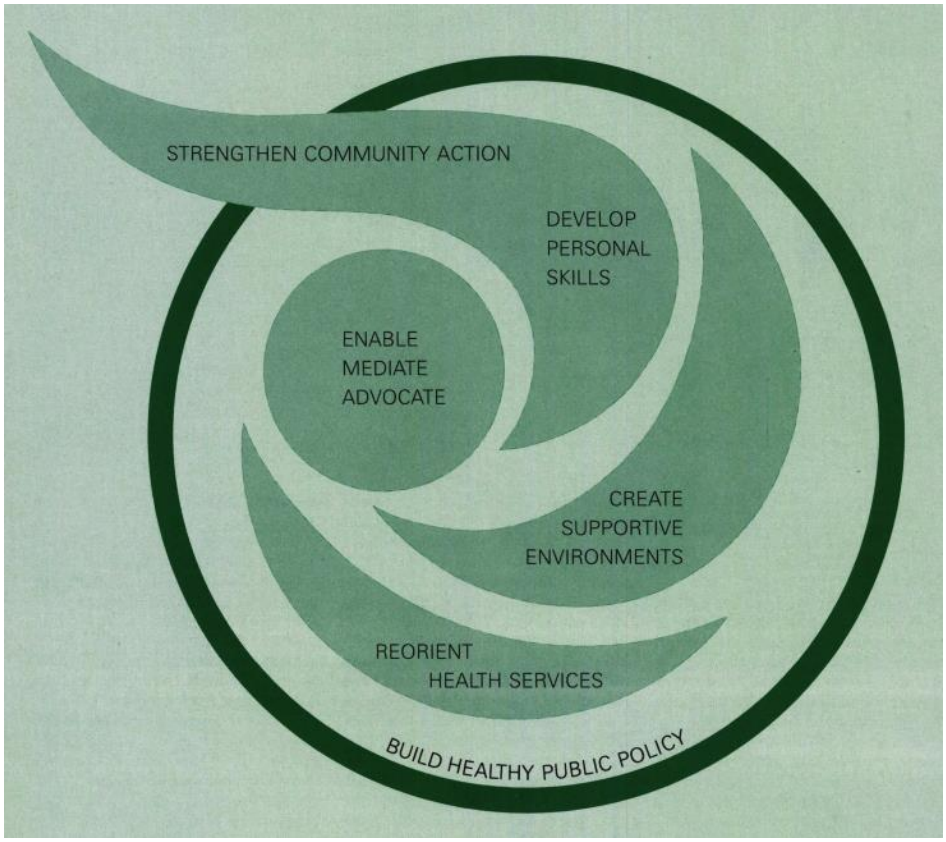



*Figure 16 - Priority actions and objectives of the Ottawa Charter (WHO, 1987)*

## Coming together to identify and scale practical solutions to improve access to CAH medicines and equipment

The world is witnessing the power of collaboration to solve childhood NCD challenges. Work to date on childhood cancer and type 1 diabetes suggests that real change is possible when we all come together.

The World Health Organisation has already played a pivotal role in promoting global efforts to protect and promote the right of children living with cancer and diabetes to enjoy the highest quality of life possible. The Global Coordination Mechanism on NCDs has done a stellar job in raising the voices of people living with NCDs. We thank WHO most sincerely for the invaluable work to date.

Regrettably, however, CAH remains a little known and neglected childhood NCD. The CAH Community cannot hope to raise the funds, awareness or support that the cancer and diabetes communities enjoy, and yet we face similar challenges and hope for similar solutions. We believe practical, sustainable and scalable solutions to the multi-faceted challenges associated with access to medicines for the CAH Community will offer hope not just to the CAH, cancer and diabetes communities, but to other childhood NCD communities as well.

@MATES4Kids commits to creating a platform that will enable a broad range of powerful stakeholders to unite and explore practical solutions. We recognise the specific recommendations from Rowlands et al. (2021) as a valuable starting point, viz:

1. Prequalification of hydrortisone and fludrocortsone medicines by WHO
2. Common registration processes for groups of countries
3. Pooled procurement, such as that offered by PAHO (Pan American Health Organization 2022)
4. Working with local pharmaceutical companies and distributors
5. Special access schemes for medicines that are not registered in countries
6. Compounded capsules or oral suspensions that offer affordable options

@MATES4Kids proposes to enable, mediate, and advocate for a holistic approach that will affect real and sustainable change. We propose a shared framework for action that addresses the five priorities of the Ottawa Charter to improve affordable access to essential medicines and equipment for the global CAH Community. Examples of specific actions we envisage are outlined in Table 2.

@MATES4Kids believes WHO holds the power and prestige needed to encourage the many necessary stakeholders to sit at the same table, discuss opportunities such as these, and collaboratively identify and commit to implementing agreed solutions. We request that WHO hosts the initiative, convenes the first meeting, and continues as a key partner leading up to the 2023 UNHLM on UHC with hosting ongoing six monthly meetings. A side event at the World Health Assembly in 2022 may be an initial opportunity.

| Action | Examples of activities | Stakeholder | Measure |
|---|---|---|---|
| Building healthy public policy | Include hc and fc on every NEML | WHO<br>Ministries of Health | % countries with hc and fc on NEML |
| | Include hc and fc within national insurance schemes | WHO<br>Ministries of Health | % countries with hc and fc on insurance scheme |
| | Ensure medicines in NEMLs are affordably available in every country | WHO<br>Ministries of Health | % countries with hc and fc available |
| Creating supportive environments | Pooled procurement | WHO, MOH & Pharma | % countries able to access hc and fc |
| | Work with pharmaceutical companies to promote access to affordable CAH medicines by all countries | WHO, MOH & Pharma | % countries able to access hc and fc |
| Reorienting health services | Mandate universal NBS (for Congenital Hypothyroidism at a minimum, with view to expansion to CAH) | WHO, MoH, IPA, APPES, APEG, GPED | % countries with NBS for CH and CAH |
| | Ensure information on CAH available in every national language | IPA, APPES, APEG, GPED | % Countries with information in local language |
| Developing personal skills | Guidelines translated into local languages and training available | IPA, APPES, APEG, GPED | % Countries with national guidelines |
| | Connect Paed Endo Societies internationally; ensure trainees in every country are supported | IPA, APPES, APEG, GPED | % Countries with national societies |
| Strengthening Community Action | Support Groups working with HCPs and MoH | CARES, CLAN, CAHSAPI, CLIP, IPA, APPES | % countries with national CAH Support Group |
| | Increase access to UHC and innovative microfinance options | WHO<br>MOH<br>NGOs | % countries with financial options for NCD families |

*Table 2 - Examples of potential solutions for discussion by stakeholders committed to equity for the global CAH Community*

# Who needs to be involved in @MATES4Kids?

## Who is currently involved?

As mentioned, expressions of interest have already been sought and confirmed from a wide range of stakeholders (Table 1) and we continue to welcome new partners to the movement.

## Who else do we need to be involved?

Representatives from the pharmaceutical industry will need to play a key role if real change is to be achieved. Ministries of health, regional WHO offices and other UN agencies would also have a role to play and we believe WHO's involvement would help the CAH Community engage powerful entities such as these.

One specific champion it would be ideal to learn more from is the Pan American Health Organization (PAHO) Strategic Fund (Pan American Health Organization 2022). The Strategic Fund offers a unique model whereby regional technical cooperation enables pooled procurement of essential medicines and equipment. There have been significant achievements by the Strategic Fund (Figure 17), and these can undoubtedly inform future initiatives to benefit childhood NCD Communities around the world. By the same token however, two-way learning and consultation may also identify some potential opportunities to strengthen the Strategic Fund with regards improving access for childhood NCD Communities.

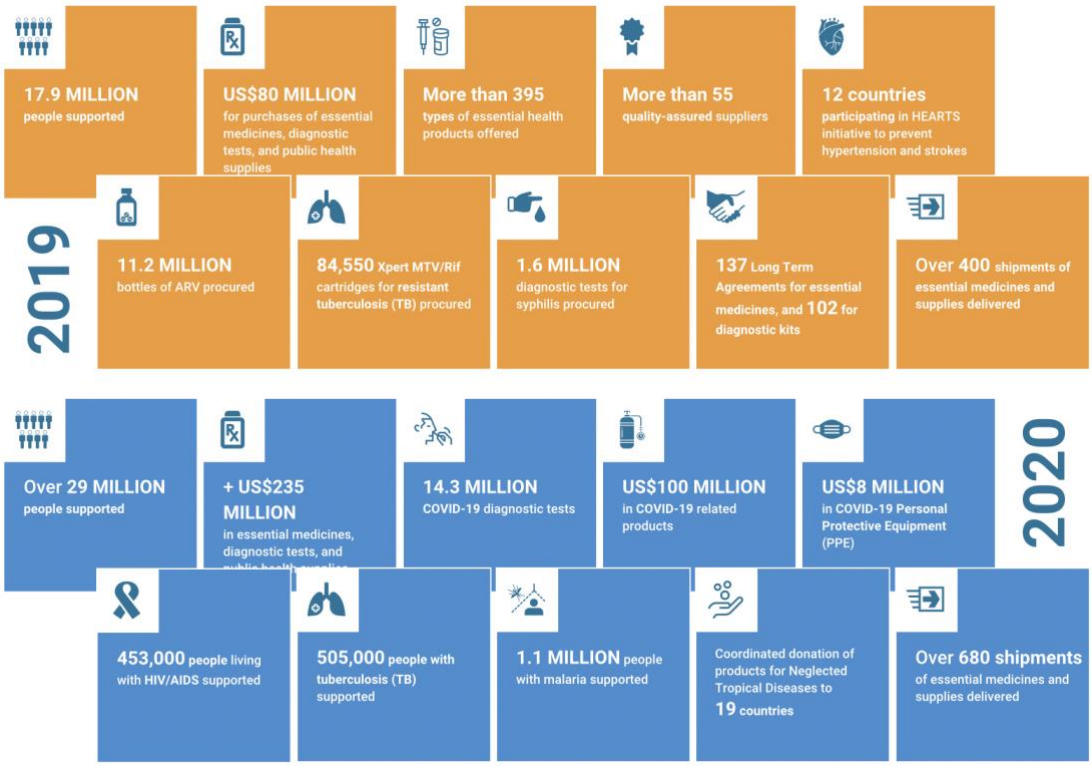



*Figure 17 - Highlights of the PAHO Strategic Fund (2019-2020) – as at September 2021*

## What is the global CAH Community asking for from WHO?

There is an urgency to this work. Children with CAH who cannot access essential medicines and equipment will die. The UNHLM on UHC in 2023 and UNHLM on NCDs in 2025 will prove invaluable milestones.

@MATES4Kids believes that WHO has a key role to play. We request support to:

a) **Attract** – Harness convening power of WHO to bring the most powerful and important players to the same table.
b) **Advocate and raise Awareness** – Opportunities to hold WHA events; include access to medicines for children in WHA agendas; promote work of group and CAH Community.
c) **Act** – Host regular meetings leading up to UNHLM on UHC & NCDs. WHO can help ensure meetings translate to critical and innovative action.
d) **Agree** – On KPIs and what success will look like; SDGs are currently no help to children.
e) **Advance accountability** – Monitor and evaluate outcomes; inclusion of hydrocortisone and fludrocortisone on WHO EMLc must translate to NEMLs in all countries.

@MATES4Kids requests WHO host a series of meetings and workshops ahead of the Second UNHLM on UHC in 2023 as we all work together to identify, implement, and monitor some practical, realistic solutions. We will use the KTA Framework to inform a continuous quality improvement approach and evaluate progress to inform changes and further actions.

We request WHO assists with hosting regular meetings (at least biannual) leading up to the UN High Level Meetings on UHC (2023) as a minimum, with a view to continue this work on to UNHLM on NCDs (2025), and again to 2030 if agreed.

And finally, we request WHO works with @MATES4Kids to urgently explore the translation of key learnings, successes and achievements in the fields of Diabetes and Cancer to benefit the CAH Community. Innovative actions, such as central registration of medicines (as has occurred for insulin) hold hope for other NCD Communities and warrant further attention.

Only by coming together do we stand a chance of reducing the global preventable mortality associated with CAH and other childhood NCDs by 30%.

## Recommendations for next steps

An initial meeting with some @MATES4Kids stakeholders and WHO was held in October 2021. The @MATES4Kides team was requested by WHO to prepare a 20+ page briefing paper which summarised the situation for the international CAH Community and outline a framework for future action. This paper is an initial attempt to fulfil this request.

We now recommend the following next steps:

- Agreement on using CLAN's Strategic Framework for Action, the Knowledge To Action (KTA) Framework and Ottawa Charter to inform a collective approach to collaborative action.
- Finalisation of this briefing paper by @MATES4Kids stakeholders, to capture and agree on the "data", clarify the "problem", and outline appropriate next steps for "discourse", "decisions" and action.
- Agreement on governance (terms of reference, timeline, roles, responsibilities). At a minimium, we request WHO host three meetings from early 2022 to September 2023 and support engagement leading up to and during the upcoming UNHLMs on UHC (2023) and NCDs (2025).
- Establishment of a Community of Practice (CoP) that will unite those committed to action for the global CAH Community to meet between WHO hosted meetings to share updates and achievements emerging from CQI initiatives.

We propose the following structure to meetings to facilitate a CQI approach:

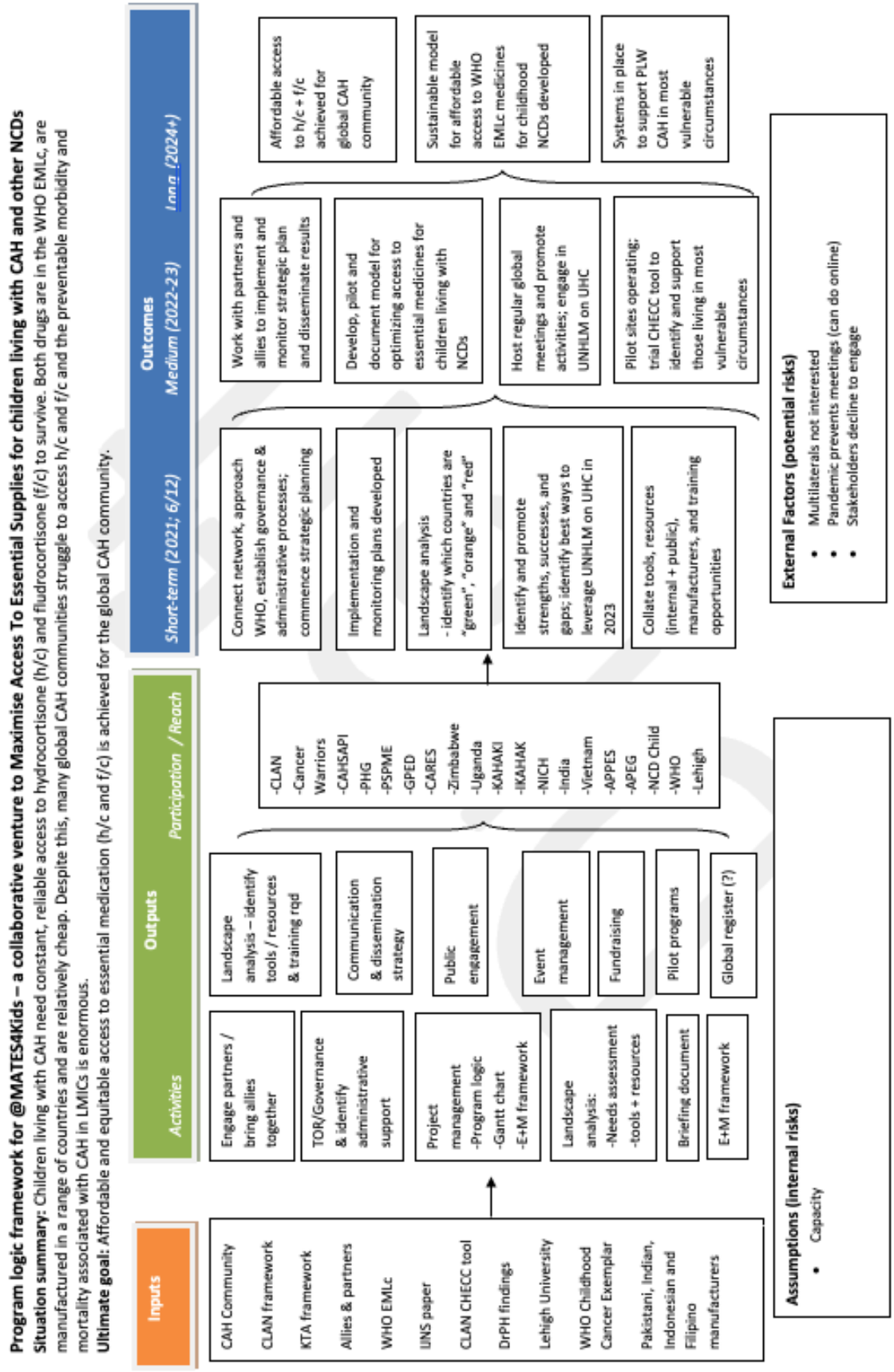
- Agree the problem (review knowledge emerging since last meeting)
- Assess data/indicators/outcomes/impact to inform appropriate next steps and agree on a program logic framework to guide next steps (initial draft for consultation is included in the Appendix).
- Agree specific actions to be next implemented
- Agree appropriate indicators for ongoing evaluation and monitoring
- Allocate actions and clarify roles and responsibilities
- Adjourn meeting to implement actions

We propose the following timeline (Figure 18):

- Inaugural meeting in early 2022
- Six monthly meetings hosted by WHO
- Quarterly Community of Practice meetings to share CQI updates and successes
- Side event at the 2022 WHA to report on action so far, and proposed next steps
- Side event at the 2023 WHA
- Final report at the 2023 UNHLM on UHC
- Agreement by all parties on next steps


*Figure 18 - Proposed timeline for action of @MATES4Kids*

# Appendix – Proposed Theory of Change to inform @MATES4Kids



## References


Abad, PJ, Anonuevo, C, Daack-Hirsch, S, Abad, L, Padilla, C & Laurino, M 2017, 'Communication about Congenital Adrenal Hyperplasia: Perspective of Filipino Families', *Journal of Genetic Counselling,* vol. 26, p. 12, DOI:10.1007/s10897-016-0043-x.

Alfadhel, M, Al Othaim, A, Al Saif, S, Al Mutairi, F, Alsayed, M, Rahbeeni, Z, Alzaidan, H, Alowain, M, Al-Hassnan, Z & Saeedi, M 2017, 'Expanded Newborn Screening Program in Saudi Arabia: Incidence of screened disorders.', *Journal of Paediatric Child Health,* vol. 53, p. 6.

Alshabab, LIS, Alebrahem, A, Kaddoura, A & Al-Fahoum, S 2015, 'Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: A five-year retrospective study in the Children's Hospital of Damascus, Syria', *Qatar Medical Journal,* vol. 2015, no. 1, DOI:10.5339/qmj.2015.11.

Armstrong, K 2021. A health needs assessment (HNA) to improve health outcomes and redress inequities for children living with nephrotic syndrome in Vietnam. Flinders University.

Armstrong, K, Henderson, C, Hoan, N & Warne, G 2006, 'Living with Congenital Adrenal Hyperplasia in Vietnam: A survey of parents', *Journal of Paediatric Endocrinology & Metabolism,* vol. 19, no. 10, p. 16.

Armstrong, K, Yap, AB, Chan-Cua, S, Craig, ME, Cole, C, Chi Dung, V, Hansen, J, Ibrahim, M, Nadeem, H, Pulungan, A, Raza, J, Utari, A & Ward, P 2020, 'We All Have a Role to Play: Redressing Inequities for Children Living with CAH and Other Chronic Health Conditions of Childhood in Resource-Poor Settings', *International Journal of Neonatal Screening,* vol. 6, no. 76, p. 31, DOI:10.3390/ijns6040076.

Baumgartner-Parzer, SM, Nowotny, P, Heinze, G, Waldhausl, W & Vierhapper, H 2005, 'Carrier frequency of congenital adrenal hyperplasia (21-hydroxylase deficiency) in a middle European population', *J Clin Endocrinol Metab,* vol. 90, no. 2, pp. 775-8, DOI:10.1210/jc.2004-1728.

Bhansali, A, Walia, R, Singh, R & Sriram, M 2009, 'Disorders of Sex Development: A Study of Ninety-Five Patients', *The Endocrinologist,* vol. 19, no. 3, p. 3, DOI:10.1097/TEN.0b013e3181a699ac.

Bukhman, G, Mocumbi, A, Atun, R, Becker, A, Bhutta, Z, Binagwaho, A, Clinton, C, Coates, M, Dain, K, Ezzati, M, Gottlieb, G, Gupta, I, Gupta, N, Hyder, A, Jain, Y, Kruk, M, Makani, J, Marx, A, Miranda, J, Norheim, O, Nugent, R, Roy, N, Stefan, C, Wallis, L, Mayosi, B, Adjaye-Gbewonyo, K, Adler, A, Amegashie, F, Amuyunzu-Nyamongo, M, Arwal, S, Bassoff, N, Beste, J, Boudreaux, C, Byass, P, Cadet, J, Dagnaw, W, Eagan, A, Feigl, A, Gathecha, G, Haakenstad, A, Haileamlak, A, Johansson, K, Kamanda, M, Karmacharya, B, Kasomekera, N, Kintu, A, Koirala, B, Kwan, G, Larco, N, Maongezi, S, Masiye, J, Mayige, M, McLaughlin, A, Memirie, S, Muquingue, H, Mwangi, K, Ndayisaba, G, Noble, C, Noormal, B, Olsen, M, Park, P, Aguilar, G, Sankoh, O, Saxena, A, Schwartz, L, Schwarz, D, Shaffer, J, Sumner, A, Doe, Z, Upreti, S, Verguet, S, Watkins, D & Wroe, E 2020, 'The Lancet NCDI Poverty Commission: bridging a gap in universal health coverage for the poorest billion', *The Lancet,* vol. 20, DOI:10.1016/S0140-6736.

Claahsen-van der Grinten, H, Otten, B, Stikkelbroeck, M, Sweep, F & Hermus, A 2009, 'Testicular adrenal rest tumours in congenital adrenal hyperplasia', *Best Practice &*

*Research Clinical Endocrinology & Metabolism,* vol. 23, no. 2, p. 11, DOI:10.1016/j.beem.2008.09.007.

CLAN Child Health 2019a, *Congenital Adrenal Hyperplasia (CAH),* CLAN INC, accessed 2022, <https://www.clanchildhealth.org/cah.html>.

CLAN Child Health 2019b, *A new resource for girls living with CAH in Indonesia!,* CLAN Child Health, accessed 16 February, <https://www.clanchildhealth.org/cah-resource.html>.

Costa de Miranda, M, Bertocco de Paiva Haddad, L, Trindade, E, Cassenote, A, Hayashi, GY, Damiani, D, Cavalieri Costa, F, Madureira, G, Bilharinho de Mendonca, B & Bachega, T 2021, 'The Cost-Effectiveness of Congenital Adrenal Hyperplasia Newborn Screening in Brazil: A Comparison Between Screened and Unscreened Cohorts', *Frontiers in Paediatrics,* DOI:10.3389/fped.2021.659492.

Daniel, R, Yadav, J, Kumar, R, Malhi, P, Sharma, A & Dayal, D 2021, 'Health-related quality of life and fatigue perception in children with congenital

adrenal hyperplasia: A Developing nation perspective', *Pediatric Endocrinology, Diabetes and Metabolism,* vol. 27, no. 4, p. 5, DOI:10.5114/pedm.2021.109269.

Gilban, D, Alves, P & Beserra, I 2014, 'Health related quality of life of children and adolescents with congenital adrenal hyperplasia in Brazil', *Health and Quality of Life Outcomes,* vol. 12.

Graham, I, Logan, J, Harrison, M, Straus, S, Tetroe, J, Caswell, W & Robinson, N 2006. Lost in knowledge translation: Time for a map? Journal of Continuing Education in the Health Professions: Journal of Continuing Education in the Health Professions.

Grosse, S & Van Vliet, G 2007, 'How Many Deaths Can Be Prevented by Newborn Screening for Congenital Adrenal Hyperplasia?', *Hormone Research in Paediatrics,* vol. 67, no. 1, p. 7, DOI:10.1159/000098400.

Halper, A, Hooke, M, Gonzalez-Bolanos, MT, Vanderburg, N, Tran, T, Torkelson, J & Sarafoglou, K 2017, 'Health-related quality of life in children with congenital adrenal hyperplasia', *Health and Quality of Life Outcomes,* vol. 15, no. 1, DOI:10.1186/s12955-017-0769-7.

Hannah-Shmouni, F, Morissette, R, Sinaii, N, Elman, M, Prezant, T, Chen, W, Pulver, A & Merke, D 2017, 'Revisiting the prevalence of nonclassic congenital adrenal hyperplasia in US Ashkenazi Jews and Caucasians', *Genetics in Medicine,* vol. 19, no. 11, p. 3, DOI:10.1038/gim.2017.46.

Kamoun, M, Feki, MM, Sfar, MH & Abid, M 2013, 'Congenital adrenal hyperplasia: Treatment and outcomes', *Indian J Endocrinol Metab,* vol. 17, no. Suppl 1, pp. S14-7, DOI:10.4103/2230-8210.119491.

Ladjouze, A, Yalaa, I, Yahiaouia, M, Zerguinia, D, Tardyb, V, Mohammedia, K, Taleba, O, Kerkouchea, S, Berkouka, K, Bensminaa, M, Maoudja, A, Abouraa, R, Ananea, T, Yves, M & Bouzerara, Z 2018, 'Age at Diagnosis and Outcome in Maghreb patients with 21-hydroxylase Deficient Congenital Adrenal Hyperplasia; Urgent need for Newborn Screening', *European Society for Paediatric Endocrinology*

Levesque, J-F, Harris, M & Russell, G 2013, 'Patient-centred access to health care: conceptualising access at the interface of health systems and populations', *International Journal for Equity in Health,* vol. 12, no. 18, DOI:10.1186/1475-9276-12-18.

Li, Z, Huang, L, Du, C, Zhang, C, Zhang, M, Liang, Y & Luo, X 2021, 'Analysis of the Screening Results for Congenital Adrenal Hyperplasia Involving 7.85 Million Newborns in China:

A Systematic Review and Meta-Analysis', *Frontiers in Endocrinology,* vol. 12, DOI:10.3389/fendo.2021.624507.

Marmot, M 2005, 'Social determinants of health inequalities', *The Lancet,* vol. 365, p. 5, DOI:10.1016/S0140-6736(05)71146-6.

Merke, D 2021. Treatment of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency in infants and children. 13/1/2021 ed. UpToDate.

Merke, D & Auchus, R 2021. Clinical manifestations and diagnosis of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency in infants and children. UpToDate.

Musa, N, Asem, N, Basyony, S & Fawaz, L 2020, 'Assessment of health-related quality of life in Egyptian children and adolescents with congenital adrenal hyperplasia', *Journal of Paediatric Endocrinology & Metabolism,* vol. 33, no. 2, p. 9, DOI:10.1515/jpem-2019-0345.

NCD Child 2022, *NCD Child,* accessed 2022, <https://www.ncdchild.org>.

New, M 2006, 'Congenital Adrenal Hyperplasia and Poverty', *Journal of Paediatric Endocrinology & Metabolism,* vol. 19, no. 10.

Padilla, C, Therrell, B, Alcausin, MML, de Castro, R, Gepte, MB, Reyes, E, Jomento, C, Suarez, RC, Maceda, E, Abarquez, C, Posecion, JEW, Andal, A, Elizaga, AL, Halili-Mendoza, B, Otayza, MP & Hoppe, C 2021, 'Successful Implementation of Newborn Screening for Hemoglobin Disorders in the Philippines', *International Journal of Neonatal Screening,* vol. 7, no. 2, DOI:10.3390/ijns7020030

Pan American Health Organization 2022, *PAHO Strategic Fund,* World Health Organisation Americas, accessed 27 February, <https://www.paho.org/en/paho-strategic-fund>.

Pang, S, Murphey, W, Levine, LS, Spence, DA, Leon, A, LaFranchi, S, Surve, AS & New, MI 1982, 'A pilot newborn screening for congenital adrenal hyperplasia in Alaska', *J Clin Endocrinol Metab,* vol. 55, no. 3, pp. 413-20, DOI:10.1210/jcem-55-3-413.

Reisch, N, Arlt, W & Krone, N 2011, 'Health problems in congenital adrenal hyperplasia due to 21-hydroxylase deficiency', *Hormone Research in Paediatrics,* vol. 76, no. 2, p. 12, DOI:10.1159/000327794.

Rowlands, A, Deeb, A, Ladjouze, A, Hamza, RT, Musa, SA, Raza, J, Jennane, F, Abu-Libdeh, A, Chanoine, J-P & GPED CAH Working Group 2021, 'Access to fludrocortisone and to hydrocortisone in children with congenital adrenal hyperplasia in the WHO Eastern Mediterranean Region: it takes a village...', *British Medical Journal Global Health,* vol. 6, DOI:10.1136/bmjgh-2021-007195.

Scott, J, Menouar, M & Dunn, R. 2021. Physiology, Aldosterone. *StatPearls* [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK470339/ [Accessed 29/10/21].

Seneviratne, SN, Jayarajah, U, Gunawardana, S, Samarasinghe, M & de Silva, S 2021, 'Gender-role behaviour and gender identity in girls with classical congenital adrenal hyperplasia', *BMC Pediatrics,* vol. 21, DOI:10.1186/s12887-021-02742-9.

Thau, L, Gandhi, J & Sharma, S. 2021. Physiology, Cortisol. *StatPearls* [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK538239/ [Accessed 29/10/21].

Therapeutic Guidelines 2021. Congenital Adrenal Hyperplasia. Therapeutic Guidelines.

United Nations 1990. United Nations Convention on the Rights of the Child.

United Nations Department of Economic and Social Affairs 2021, *The 17 Goals,* United Nations, accessed 5 November, <https://sdgs.un.org/goals>.

Verhees, M, Engels, M, Span, P, Sweep, F, van Herwaarden, A, Falhammar, H, Anna, N, Webb, E, Richter-Unruh, A, Bouvattier, C, Brac de la Perrière, A, Arlt, W, Reisch, N,

Köhler, B, Rapp, M, Stikkelbroeck, N, Roeleveld, N & Claahsen-van der Grinten, H 2021, 'Quality of Life in Men With Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency', *Frontiers in Endocrinology,* DOI:10.3389/fendo.2021.626646.

Warne, G 2008, 'Long-term outcome of disorders of sex development', *Sexual Development,* vol. 2, no. 4-5, p. 5, DOI:10.1159/000152043.

Watson, M, Mann, M, Lloyd-Puryear, M, Rinaldo, P & Howell, RR 2006, 'Newborn screening: toward a uniform screening panel and system', *Genetic Medicine,* DOI:10.1097/01.gim.0000223891.82390.ad.

White, P 2009, 'Neonatal screening for congenital adrenal hyperplasia', *Nature Reviews Endocrinology,* vol. 5, no. 9, p. 8, DOI:10.1038/nrendo.2009.148.

World Health Organisation 2013. Global Action Plan for the Prevention and Control of Noncommunicable Diseases. Geneva, Switzerland: World Health Organisation.

World Health Organisation 2020. The selection and use of essential in vitro diagnostics. Geneva: World Health Organisation,.

World Health Organisation 2021. WHO Model List of Essential Medicines for Children - 8th List. Geneva, Switzerland: World Health Organisation.

World Health Organisation 2022a, *Child Growth Standards,* World Health Organisation, accessed 16 February, <https://www.who.int/tools/child-growth-standards/standards>.

World Health Organisation 2022b, *UHC Compendium,* World Health Organisation,, accessed 16 Feb, <https://www.who.int/universal-health-coverage/compendium>.

World Health Organisation Adopted by the International Health Conference in New York, USA on 22 July 1946, and came into Force on 7 April 1948. Constitution of the World Health Organisation. World Health Organisation.

Wu, J, Sudeep, D, Harris, M, McGown, I & Cotteril, A 2011, 'Is it time to commence newborn screening for congenital adrenal hyperplasia in Australia?', *Medical Journal of Australia,* vol. 195, no. 5, p. 2, DOI:10.5694/mja11.10284.

Zainuddin, A, Grover, S, Shamsuddin & Mahdy, Z 2013, 'Research on Quality of Life in Female Patients with Congenital Adrenal Hyperplasia and Issues in Developing Nations', *Journal of Pediatric Adolescent Gynaecology,* vol. 26, p. 8.