Increasing access to essential medicines through partnership:

experience in developing and delivering chlorhexidine for newborn cord care

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Increasing access to essential medicines through partnership

The journey of chlorhexidine

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HELPING TO SAVE ONE MILLION CHILDREN'S LIVES

Newborns in resource-limited countries, where births frequently occur at home without trained healthcare workers, are particularly susceptible to infection through the newly cut umbilical cord. Use of chlorhexidine digluconate (CHX) for umbilical cord care can help to prevent infection

2011

WHO list CHX as a priority medicine

CHX listed by the WHO as a priority medicine for children's health, requiring further R&D

2012

UN call to action

UN Commission identified CHX as a life-saving commodity for women's and children's health

UN called for additional manufacturers to supply high-quality, affordable CHX for newborn cord care that, with widened access across 50 resource-limited countries, could save 422,000 lives over 5 years

GSK began to reformulate their existing CHX product into a gel suitable for use in resource-limited settings

2013

A partnership with a mission

Partnership established between GSK and Save the Children (STC) to find new ways to reduce childhood mortality from preventable and treatable diseases

2014

Partnerships in action

The Chlorhexidine Working Group began coordinating approaches to advancing use of CHX for umbilical cord care via a collaboration with manufacturers, international NGOs, governments and universities

STC and others worked with the Kenyan Ministry of Health to develop national guidelines on the use of CHX for cord cleansing

2016

Positive opinion by the EMA

Following accelerated review, GSK's CHX gel was granted a positive opinion by the EMA, facilitating approval in 19 countries, including Kenya (in 2017)

Managed Access Programme (MAP) established in Kenya

GSK and STC partnered to implement a MAP in Kenya, which ran to 2018. Insights from healthcare worker interviews, user focus groups and informal local feedback informed the CHX gel formulation, packaging and patient information materials developed by GSK

Acceptability of CHX gel was very high (99%) from both service providers (n=39) and mothers (n=479) and 92% of mothers (n=479) stated they would recommend the product to other mothers

2018

Learnings shared

Learnings from the Kenyan MAP successfully applied to a 2-year CHX implementation research project in Papua New Guinea. Agreement with USP/USAID established with aim to transfer CHX technical know-how to LMICs

2021

CHX supplied locally and widely used

GSK stopped manufacturing CHX gel because generic manufacturers are now supplying affordable product in sufficient volumes to meet local demand

Locally-manufactured CHX is now available in all counties in Kenya and 43% of all newborns receive the protection provided by CHX

ACCESS TO ESSENTIAL MEDICINES: CHLORHEXIDINE DIGLUCONATE

- Availability
- Affordability
- Acceptability
- Accessibility

Ilan Godfrey / Save the Children

INTRODUCTION

Medicines can only be used to their full potential if robust and equitable healthcare systems are in place, in order for the medicine to reach the patient. Barriers to access can be evaluated through an Access to Medicines (ATM) framework of availability, affordability, acceptability, and accessibility, also known as the 4A framework.[1] The United Nations (UN) recognises the importance of essential medicines within its Sustainable Development Goal (SDG) 3 (Good Health and Well-Being) in targets 3.8 – achieving universal health coverage (UHC), striving for a world where all people have equitable access to quality, essential healthcare without risk of financial hardship – and 3.B – supporting the research and development (R&D) of vaccines and medicines for diseases primarily affecting resource-limited countries.[2]

Overcoming obstacles to ensure sustainable access to essential medicines in low- and middle-income countries (LMICs) requires innovative cross-sectoral collaboration throughout the lifecycle of a medicine. The past 2 decades have seen an increase in the number of public, private and civil society partnerships at the national and supranational levels, underpinning approaches aligned to the UN's SDG 17 to "revitalize the global partnership for sustainable development",[3] more specifically to "encourage and promote effective public, public–private and civil society partnerships, building on the experience and resourcing strategies of partnerships".[3]

Partnerships can leverage the complementary expertise of different partners and ensure sustainability of global health products, whilst also helping to share risks. Maintaining the required level of investment for the R&D, manufacture, commercialisation and supply of new treatments for conditions predominantly affecting LMICs is challenging. The traditional pharmaceutical R&D business model is based on anticipated return via new product sales, thus incentivising companies to undertake lengthy and costly R&D processes. Recovering investment is more challenging and collaborations with other global and national stakeholders is important to ensure sustainable and affordable access.

Overcoming obstacles to ensure sustainable access to essential medicines in LMICs requires innovative cross-sectoral collaboration throughout the lifecycle of a medicine

Given the importance of partnership across sectors to address the systemic challenges of global health and health inequity, it is timely to reflect on one approach taken in the development and supply of chlorhexidine digluconate 7.1% w/w gel ([CHX] equivalent to 4% w/w chlorhexidine) for neonatal cord care. We describe and analyse the steps taken by GSK to increase access, including partnering with the international non-governmental organisation (I-NGO) Save the Children (STC) in Western Kenya. Learning points gained on the journey are shared, together with subsequent steps taken to increase access, with the aim of making recommendations that may be applicable to similar enterprises in the future.

ACCESS TO ESSENTIAL MEDICINES: CHLORHEXIDINE DIGLUCONATE

Newborns in resource-limited countries, where births frequently occur at home without trained healthcare workers, are particularly susceptible to infection as the newly cut umbilical cord is a common bacterial entry point.[4] Consequently, the World Health Organization (WHO) recommends application of CHX for newborns born at home in settings with high neonatal mortality rates (>30 deaths per 1,000 live births), or as a replacement for harmful traditional substances.[5]

In 2011, CHX was listed by the WHO as one of the priority medicines for children's health requiring further commercial development of an optimal, regulatory approved, quality product;[6] and, in 2012, the UN Commission on Life-Saving Commodities identified CHX for newborn cord care as one of 13 life-saving evidence-based commodities for women's and children's health.[7]

Work to develop and make CHX gel more widely available for newborn umbilical care had been emerging in South Asia, particularly Nepal, within a public–private partnership between the Nepal Ministry of Health and Population (MoHP), a Nepali manufacturer Lomus Pharmaceuticals, and the I-NGO John Snow Inc., supported by the United States Agency for International Development (USAID). Field trials of CHX gel were undertaken in 2008–2009; the MoHP approved national scale-up in 2011. By 2013, CHX gel was in use in 36 of the 75 districts of Nepal.[8]

However, manufacturing capacity was limited and the UN called for additional manufacturers to supply high-quality, affordable CHX that, with widened access across 50 resource-limited countries, could save 422,000 neonatal lives over 5 years.[7] In response, in early 2012, GSK set out to develop a CHX gel suited to resource-limited country settings that could pass stringent regulatory review, setting a quality benchmark and filling any potential supply gaps. The Chlorhexidine Working Group (CWG), led by the non-profit organisation PATH, coordinated approaches to advancing the use of CHX for umbilical cord care across an international collaboration of organisations (from 2014 to 2017), including manufacturers, I-NGOs, governments and universities, all of whom were committed to advancing the use of CHX through advocacy and technical assistance.

GSK's ambitions were to:

- produce a stringent regulatory authority (SRA) approved, quality CHX product, available not-for-profit, for use in resource-poor settings;
- increase access, awareness, capacity and demand for CHX products to improve postnatal care for babies born in these settings, with the potential to reduce the incidence of umbilical cord infection and in turn help to avoid preventable neonatal deaths;
- encourage local manufacturers to increase global CHX capacity and supply through making manufacturing know-how available.

WHO recommends application of CHX for newborns born at home in settings with high neonatal mortality rates (>30 deaths per 1,000 live births), or as a replacement for harmful traditional substances[5]

Since the development of CHX gel, there has been a marked increase in the global supply of CHX by generic manufacturers who are now supplying affordable product in sufficient volumes to meet demand.[9] This is a positive trend that GSK fully supports; as such, in 2021, GSK made the decision to discontinue manufacturing CHX gel. This is illustrative of GSK's approach to global health, leading with its science, aligning its approach to the evolving real-world context and collaborating with organisations who have the required capabilities and infrastructure to enable increased affordability and access.

Availability

At the time of the UN call, CHX was an active ingredient (at lower concentrations) in one of GSK's consumer healthcare products, such that GSK had extensive technical knowledge of the molecule. This enabled accelerated development of GSK's CHX gel, which moved from concept to positive opinion from

the European Medicines Agency (EMA) Committee on Human Medicinal Products in 3 years and 7 months. A published CHX gel formulation[10] was optimised, reformulated into a heat-stable gel without the need for preservatives and packaged in single-use sachets. Control strategies were developed to minimise formation of impurities, in particular the potential human carcinogen 4-chloroaniline.[11] Manufacturing and analytical techniques were kept as simple as possible to facilitate local production by third parties.

The efficacy of CHX 7.1% solution for newborn cord care was supported by three previously published community-based randomised controlled trials in South Asia, and a non-inferiority study (CHX gel vs solution) for antimicrobial efficacy.[12–15] In the regulatory dossier, GSK supplemented these data with literature reviews of clinical and non-clinical safety information.

In Kenya, neonatal mortality contributes to >40% of child deaths,[17] and infection is a leading cause.[18] Improper cord hygiene has a strong positive association with neonatal sepsis. Observing good cord care practices could avert up to 67% of newborn infections[19]

In vitro tests were performed on the CHX gel: antibacterial equivalency (to ensure CHX gel works in the same manner and has the same antimicrobial activity as existing products) and skin irritancy (to ensure CHX gel is safe for newborn skin). A full Chemistry, Manufacturing and Controls data package was included to support product quality. No new clinical trial data or in vivo non-clinical study data were submitted.

Regulatory review using the EMA Article 58 pathway (intended for products to be marketed exclusively outside the European Union) in collaboration with the WHO was pursued. CHX gel was granted a positive opinion by the EMA in April 2016 via an accelerated review[16]; the resulting certificate of pharmaceutical product supported national registrations in 19 countries.

Following EMA approval, GSK focused on making CHX gel available predominantly in countries with clear medical need where there was no existing, reliable supply.

The Managed Access Programme in Kenya

In Kenya, neonatal mortality contributes to >40% of child deaths,[17] and infection is a leading cause.[18] Improper cord hygiene has a strong positive association with neonatal sepsis. Observing good cord care practices could avert up to 67% of newborn infections.[19] Awareness of CHX for cord care in Kenya was promoted by multi-agency advocacy and sensitisation work on UN-defined Life-Saving Commodities.[7] The Kenyan Ministry of Health (MoH) requested early access to CHX gel in preparation for national scale-up. In response, GSK partnered with STC to implement a Managed Access Programme (MAP) to better understand the acceptability of CHX among healthcare providers and users in health facilities in Bungoma County, Kenya.[20] The Kenyan MoH request was made even though neonatal mortality rates in Kenya in general, and in Bungoma County specifically, were below the WHO threshold[21] (20.3 and 22.1 neonatal deaths per 1,000 births, respectively)[22], when the MAP started in February 2016; however it was reported that harmful substances were still routinely applied to the cord. Subsequent qualitative research confirmed that local practice commonly included application of non-medicinal, harmful substances to the cord following births at home,[23] highlighting a need for greater awareness of appropriate newborn cord care. However, health policy at the time (and currently) prohibited the distribution of CHX by community health workers, highlighting one of the challenges of implementing global policy recommendations effectively at country level, particularly in the 2020–2021 context of a COVID pandemic, as more mothers may give birth at home because of disruptions to health services.

The MoH led the development and dissemination of national guidelines and updated the Kenyan essential medicines list (EML) to include CHX.[24] GSK's CHX gel was granted accelerated review by the Kenyan regulatory authority and was approved in May 2017. Initial access prior to national registration through the MAP was designed to inform later decision-making and ran from February 2016 to July 2018.

The objectives of the MAP were to:

1. independently assess the level at which healthcare workers and mothers in Bungoma County accepted use of CHX gel for umbilical cord care;
2. examine the factors (including enablers [e.g. preparatory training] and challenges) that influenced the provision of CHX gel for cord care by healthcare workers and subsequent uptake among mothers;
3. determine the acceptability and uptake of information, education and communication materials on CHX gel, which were developed by the MoH, among providers and mothers in the county.

CHX gel was supplied by GSK, and the programme was implemented independently by STC in conjunction with the Bungoma County MoH, the NGO Population Council was responsible for qualitative and quantitative data capture and analysis.

CHX gel was initially introduced into 21 health facilities in Bungoma County with a programme of healthcare worker training and education, including adverse event (AE) training, highlighting the importance of reporting safety information. The programme was extended to include 7 facilities managed by faith-based organisations, ultimately reaching >30,000 babies across 28 facilities.

STC, in partnership with the Bungoma County Department of Health, facilitated the collection of insights on user experiences and practices. Analysis of user acceptability showed overwhelming (99%) acceptance for use of the product by healthcare workers and mothers[20] – see key findings and recommendations in the **Acceptability section**. Advocacy and sensitisation work by STC and other partners contributed to the development of national guidelines, healthcare worker and pharmacist training, development of educational materials and job aides and the inclusion of CHX in the *Mother and Child Health Handbook*, a parent-held record of vaccination, growth and advice, offered in Kenya to all new parents.[25] Local advocacy led Bungoma and Busia Counties to incorporate CHX for cord care into their EML (devolved to county level) and ensured funds were earmarked to support routine procurement of locally manufactured CHX beginning in 2019 through the national supply chain system (Kenya Medical Supplies Authority [KEMSA]) thereby encouraging sustainability.

In October 2016, after the MAP had begun, 2 clinical studies from Tanzania and Zambia[26,27] were published that showed no statistically significant difference in neonatal mortality between CHX and dry cord care (DCC), in contrast to the results of three earlier community-based studies conducted in South Asia (Bangladesh, Pakistan and Nepal).[12–14] Although the Tanzania and Zambia studies did not show a statistically significant neonatal mortality benefit, the significant reduction in umbilical cord infection was consistent with that found in the South Asia studies. It is worth noting that in the Tanzania and Zambia studies, more women chose a hospital/clinic setting delivery, a similar scenario to Kenya to date, and overall neonatal mortality rates were much lower than expected based on national estimates. This is likely to reflect welcome improvements in integrated perinatal care in Tanzania and Zambia.

The accompanying commentary in *The Lancet Global Health*[28] used published data from all 5 studies to assess the relationship between mortality and home delivery rates, among other factors. Based on their findings, they recommended no change to existing WHO guidelines for cord care, which support CHX use for infants following home birth in regions with high neonatal mortality, and DCC for infants following facility births or home births in regions with lower neonatal mortality.

Affordability

Product development

CHX is a known active ingredient in GSK products, and clinical data from 3 independent studies demonstrating the efficacy of CHX in prevention of omphalitis had been published. Therefore, a substantial part of the R&D investment had already been made, reducing the potential risks and overall costs associated with CHX gel development. This is an important factor for a global health product like CHX that is only sold in resource-limited countries. The intent for GSK's CHX gel was to make the product available not-for-profit in countries where there was no local manufacturer or where there were issues with reliability or quality of supply.

Working with an organisation like USP greatly facilitates the transfer of technical and quality know-how to multiple local manufacturers, allowing efficient resource use and enhancing sustainability, while complying with quality standard.

Manufacturing and supply

At the outset, GSK aimed to make manufacturing know-how available[10,29] to attract other parties to manufacture the gel without the need for costly upfront investment in R&D. GSK established an agreement with United States Pharmacopeia (USP) through the Promoting the Quality of Medicines programme funded by USAID,[10] which aimed to transfer the technical know-how to a team of experts dedicated to helping LMICs strengthen the quality, manufacturing and regulatory systems that are required to ensure the quality and increase the supply of essential medicines. GSK has made the formulation dossier fully available (see https://www.usp.org/sites/default/files/usp/document/our-impact/pqm/gsk-chx-gel-tech-transfer-report-6-20-2019.pdf). Working with an organisation like USP greatly facilitates the transfer of technical and quality know-how to multiple local manufacturers, allowing efficient resource use and enhancing sustainability, while complying with quality standard.

Economic assessment

Despite the potential life-saving benefits of widespread implementation of CHX for cord care, minimal analysis investigating the financial implications of CHX use has been conducted. We developed a cost-consequence model to assess health outcomes and resource savings associated with implementing locally manufactured generic CHX gel for neonatal umbilical cord care versus DCC in a Kenyan birth cohort. The economic outcomes were determined based on direct, indirect and total costs of care associated with omphalitis. The model estimated that, over 1 year, ~23,000 omphalitis cases per 500,000 births could be avoided through CHX application versus DCC, circumventing ~13,000 outpatient visits, ~43,000 bed days and preserving ~114,000 workdays. CHX was associated with annual direct cost savings of ~590,000 US dollars (USD) versus DCC (not including drug-acquisition cost), increasing to ~2.5 million USD after including indirect costs (productivity, notional salary loss).[30]

Acceptability

To address acceptability barriers related to literacy and other demographic considerations, insights from healthcare worker interviews, user focus groups and informal local feedback (obtained by STC, the CWG and local regulatory authorities) were used to inform the CHX gel formulation, packaging and patient information leaflet developed by GSK. Insights gathered during development suggested that a gel rather than liquid formulation would increase ease of use, echoing similar developments in South Asia, and a sachet with pictorial instructions would facilitate correct usage in low-literacy settings. The single-use sachet, available in single or 7-day packs to suit local regulations for cord care,[31] was designed to be opened without scissors and to deliver the correct dose. Subsequent market research (from both stakeholders and patients) following the development of the product indicated that satisfaction with the tube options was adequate, and demand for a sachet was limited.

The MAP provided the platform for a user acceptability study, undertaken by the Population Council with support from STC,[23] which evaluated CHX gel acceptance by healthcare workers and mothers by examining factors influencing its use and uptake. The study also assessed the acceptability of associated information, education and communication materials (e.g. a training video). The study gauged readiness for CHX gel and provided detailed evidence to support its effective introduction and subsequent efforts advocating for national scale-up.

Insights gathered during development suggested that a gel rather than liquid formulation would increase ease of use

One finding from the study was the importance of community empowerment in improving and maintaining interventions advancing positive health outcomes, particularly when the intervention disrupts cultural practices. Community engagement also provides an opportunity to educate end users who can then demand appropriate healthcare services, particularly when healthcare systems depend on “pull rather than push” procurement for health commodities.

Education and training to ensure acceptability and appropriate use

CHX has an extensively characterised safety profile from >60 years of use and chlorhexidine digluconate is in use in other products in different concentrations and settings; however, prevention of newborn cord infection was a new indication for GSK, and CHX gel was a newly approved formulation. Therefore, STC used GSK AE awareness materials to train healthcare workers on the MAP via a train-the-trainers model. Following the initial training in 2016, a few AEs were reported; however, repeat training sessions were required to remind healthcare workers of the need for continued AE reporting. In total, 24 AE reports were received (including cases of rash, delayed cord healing and cord colour change); this is consistent with the minimal safety concerns associated with CHX and shows that basic AE awareness sessions and simple reporting options can facilitate collection of safety information in settings with limited prior experience.

Although the Medicines and Healthcare Products Regulatory Agency and US Food and Drug Administration highlight the risk of rare but serious allergic reactions with antiseptic products containing chlorhexidine digluconate,[32,33] no such reports have been identified for CHX gel to date. In 2019, however, the WHO issued a CHX safety alert following at least 40 recorded incidents, across 9 sub-Saharan countries, of some CHX solution and gel products being mistaken for eye ointment or drops, leading to corneal scarring and, in some cases, blindness.[34] There were no reports of off-label use or misuse with GSK’s product. This safety alert reinforced the need for education and training for appropriate use and the importance of the differential packaging of the product and patient information. However, the safety alert, together with data from the two previously described clinical trials in African countries,[26,27] have contributed to hesitancy among some governments to implement CHX more widely despite the successful introduction and long-term use in some South Asian countries.

Key findings and recommendations from the Kenya MAP[20]

- Findings indicate an overwhelming acceptance for use of the CHX gel for cord care both from service providers (n=39) and mothers (n=479)
- 99% of mothers provided with CHX gel used it, and 97% applied it to their newborn's umbilicus daily.
- Most mothers found it easy to use, and 94% stated they were satisfied or very satisfied.
- 82% found the information they were given to take home (product inserts) very useful.
- 70% said that healthcare providers were their main source of information on umbilical cord care.
- 92% of mothers who used the product reported that they would recommend it to their friends and to other mothers as it was free, easy to use, did not affect the baby and made the cord heal quickly.
- Some healthcare practitioners reported that it was challenging to reach mothers who had delivered at home.
- Adequate preparation before roll-out for community sensitisation and health worker training is essential.
- Communication materials, job aids and product inserts should be as user friendly as possible.

Accessibility

In 2014, the Kenyan MoH began to standardise the approach to newborn cord care, working with STC and others to develop national guidelines on the use of CHX for cord cleansing within 24 hours of birth,[35] as well as healthcare worker training materials and job aids in preparation for roll-out. STC was also involved in high-level advocacy efforts that led to the inclusion of CHX in the Kenyan EML,[24] a major step in promoting regular supply to healthcare facilities through national supply mechanisms. However, government policy restricted the use of CHX to trained healthcare facility workers only; therefore, babies born at home had to be brought to a healthcare facility to receive CHX, delaying access.

An additional challenge was presented by a prolonged healthcare worker strike lasting >100 days (May–October 2017) during the MAP, resulting in significant disruption to healthcare delivery. STC instituted measures to reduce the impact on access and potential waste of CHX gel, including redistributing CHX gel to facilities with the most births and where healthcare workers were available to educate mothers on correct application and expanding the MAP to include 7 facilities from the faith-based sector.

Kenya began decentralising its healthcare services in 2013, giving local authorities more autonomy in setting the healthcare agenda in their county.[36] Implementing the MAP within a newly established decentralised healthcare system required close engagement with national and local government stakeholders to support the adoption of national policy. Successful implementation of the MAP is attributable to the collaborative partnership between GSK, STC and the county director of health.

Building on the success of the MAP and to drive towards sustainable scale-up and access of CHX for newborn cord care in Kenya, STC supported Amref Health Africa on a GSK-funded project to contribute to the MoH's mission to achieve UHC. A study in Kwale, Vihiga and Machakos counties conducted by Amref Health Africa in 2019 identified key barriers to CHX access which included inconsistent knowledge on its use and poor supply chain management resulting in prolonged stock-outs. These findings informed awareness activities designed to strengthen knowledge and skills of healthcare workers at health facility and community levels on the correct usage of CHX and of supply chain management at all levels to prevent stock-outs and enable effective scale-up of CHX. Working in partnership, Amref Health Africa, STC, the Kenya MoH (Division of Neonatal and Child Health) together with engagement from the County First Ladies Association[37] conducted roundtable discussions at national and county levels to develop information, education and communication materials and a policy brief to create awareness of CHX.

Successful implementation of the MAP is attributable to the collaborative partnership between GSK, STC and the county director of health

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LESSONS LEARNED

- Product development
- Regulatory environment
- Pharmacovigilance
- Creating an enabling environment
- Country financing
- Applying learnings to other settings

LESSONS LEARNED

A set of conducive environmental factors paved the way for the rapid development of CHX gel for use in LMICs. As a long-established, non-proprietary antiseptic with existing clinical data and extensive use in South Asia for umbilical cord protection, CHX presented a viable opportunity for GSK to develop an alternative formulation to meet an unmet need. To work beyond the limitations of the traditional pharmaceutical R&D business model, innovative approaches, including working in partnerships, was required.

Product development

Throughout product development, gaining insights from users and learning from partners experienced in settings in which CHX gel would be used was critical in optimising its acceptability. Through participation in the CWG, convened by PATH, which included local manufacturers and I-NGOs, GSK gained insights from the group around packaging, country prioritisation and unmet need, and were able to share their knowledge with the group, for example, around product quality and pharmacovigilance. Insights from the CWG contributed to the decision to package CHX gel in single-use sachets to facilitate ease of use and avoid retention of excess gel for alternative uses, and to include pictorial instructions on the sachet and secondary packaging to reinforce appropriate use, in low literacy settings. Generating such insights early in the development pathway is recommended for similar future endeavours.

The manufacturing process was developed to be as simple as possible and easily transferable to local manufacturers, maintaining rigorous quality standards and minimising impurities. Initial insights indicated the value of a sachet; however, subsequent market research identified that current product options are adequate and demand for a sachet was limited, thus it is not only important to gather insights when initially developing a product but throughout a product lifecycle. Spontaneous uptake has been slow underlining the need for proactive strategies to engage with local manufacturers to stimulate demand and interest in new products.

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Regulatory environment

EMA registration via Article 58 enabled fast-track regulatory assessment and guaranteed stringency and quality assurance. EMA approval and availability of the certificate of pharmaceutical product was followed by national regulatory approvals; however, the national regulatory process took >2 years in some cases. Humanitarian organisations are often the primary procurers of essential medicines in LMICs; and, although they do not commonly require national regulatory approval to import or distribute drugs, they adhere to strict quality standards for the medicines they procure, often relying on a product being approved by a stringent regulatory authority or a manufacturer complying with UN or WHO quality standards. Humanitarian organisations therefore tend to use waivers to enable them to rapidly deploy a commodity when it is needed while maintaining the highest quality standards. Despite this, national authorities frequently prefer to import products that are approved in their own countries; this also builds the capability of local regulators. Gaps in the process created further obstacles downstream that could be improved in future; most notably, alignment between the EMA and the WHO. For example, a positive opinion via EMA Article 58 process does not automatically result in WHO prequalification or inclusion in the EML.

Pharmacovigilance

Pharmacovigilance is important when introducing a new medicine in a resource-limited country where AE reporting mechanisms are not robust. As more medicines are developed in response to diseases of the developing world, sustainable AE reporting is globally recognised as a concern.

A low-intervention pharmacovigilance training model, jointly disseminated by GSK and STC in Kenya, successfully generated limited short-term safety information for CHX gel. This was proportionate to the controlled environment of a MAP and the well-established safety profile of CHX provided reassurance regarding the safety profile of CHX gel. Further improvements in underlying healthcare systems and new multi-stakeholder initiatives such as the WHO Project 3-S[38] should allow implementation and adoption of pharmaco-vigilance structures, enabling local stakeholders to play a greater role in long-term safety monitoring for all products.

Creating an enabling environment

The integration of a new commodity in a low-resource setting with traditional customs, as is the case for umbilical cord care, is a complex process. Changing knowledge, attitudes and practices were required at all levels. A top-down approach from the government alone is frequently insufficient for a product to be adopted and accepted. Successful adoption may often be better driven by community-level pull; therefore, it is essential to educate end-users who then demand appropriate access to product and healthcare services. Although GSK did not pursue access to CHX gel through private sector channels, such as pharmacies and clinics, this could be considered for future endeavours as an important mechanism for extending accessibility and for generating demand and awareness in the public sector.

In Kenya, although health policy, guidance and recommendations are led from central government and the MoH, much of the decision-making and budget allocation within the healthcare system is devolved to county-level governments and supported by local MoH officials. Although there are some benefits to this model, it also increases the number of decision-makers, discussions needed, time and complexity of introducing or scaling up any intervention or change in policy.

STC leveraged its experience in navigating the different intersections of national and local government, engaging decision-makers at all levels and implementing behaviour change programmes to encourage use of CHX and reduce harmful cord practice

A major challenge was the absence of policy and guidelines at national level for CHX use. Despite positive findings of the MAP programme, a relatively supportive policy environment and the availability of locally manufactured product in Kenya, CHX products still fail to reach newborns most vulnerable to the highest risk of neonatal death owing to insufficient funding, and policies that inadvertently prevent CHX from easily reaching babies born at home. This highlights the importance of driving towards UHC, ensuring that healthcare policies do not conflict and promoting equal access to maternal and neonatal care.

Clinical guidelines and training materials were developed that helped address healthcare workers' concerns on the use of CHX. These were also critical in advocacy efforts to get buy-in from senior leadership at county level for implementation of the MAP. STC leveraged its experience in navigating the different intersections of national and local government, engaging decision-makers at all levels and implementing behaviour

change programmes to encourage use of CHX and reduce harmful cord practices. This is where trusted partners on the ground, who are knowledgeable of and can work effectively with the spectrum of key stakeholder groups, are essential to ensure the needs of communities are best addressed and access best supported.

Sustained community engagement

Changes in recommendations on cord care over the years have made it difficult to implement and adhere to a new practice. Increased community and healthcare worker awareness and acceptance of CHX compared with the current standard of care in the facilities covered by the MAP were essential in driving the uptake of its use. Sustained community engagement and sensitisation, including counselling by healthcare workers, were critical to build trust and overcome deep-rooted sociocultural beliefs and practices that were barriers to uptake at the household level, especially because of the cultural influences surrounding cord care from many members of the community (e.g. men, traditional birth attendants, mothers-in-law). Word of mouth and peer-to-peer influence are important mechanisms for promoting behaviour change in communities, especially when driven by those who have first-hand experience with CHX.

Country financing

The uptake of all CHX products for cord care has been slow in high-need countries. In Kenya, this is as a result of many factors, including competing county demands and inadequate resources. Limited funding for essential medicines, a challenge in many LMICs, has delayed the national scale-up of CHX in Kenya and in many other countries where it is often necessary to prioritise one medicine over another on an EML owing to limited funding. Although LMICs generally spend more of their gross domestic product on pharmaceuticals than high-income countries, the per capita spend and proportion coming from public expenditure is lower; therefore, out-of-pocket expenses are higher.[39] With strong price pressure from institutional customers, price remains the primary driver of product adoption for governments. The GSK manufactured/branded CHX product is significantly more expensive than regional manufacturers, even at our not-for-profit price, given GSK's manufacturing costs. In many LMICs, the MoH relies on donors and development partners to supplement funding. Whereas partners were forthcoming during the early, 'innovative' stages of the project, engagement fell as the focus transitioned to funding flows and establishing national procurement systems, limiting penetration. Supply chain fragmentation and the absence of awareness and demand-generation activities also contributed to the slow uptake. This highlights the need for a continuous sustained long-term effort to ensure uptake of an essential medicine.

Access to locally manufactured CHX for the facilities in this programme is now possible through KEMSA, in line with the project vision. However, although CHX is on the Kenyan EML and included in neonatal care guidelines, it is unclear whether neonatal mortality rates will influence sustained political commitment to scale-up, given that, in 2019, many counties are below the WHO threshold of 30 deaths per 1,000 live births.

Applying learnings to other settings

Learnings from the Kenya programme were applied to a CHX implementation research project in Papua New Guinea (PNG) from December 2018 to March 2020, led by the Burnet Institute and the Provincial Government and National Department of Health under the Healthy Mothers, Healthy Babies programme[40] and supported by GSK. As with Kenya, PNG has a relatively supportive newborn health policy. CHX is mentioned in the national standard treatment guidelines as part of cord care for all newborns, particularly those born outside of health facilities; however, it is not yet incorporated into standard medicines lists or procurement and supply systems.

Similar to the Kenya MAP, the Burnet PNG project addressed two needs: the dissemination of information and educational tools relating to the postnatal period and implementation research into how to best introduce CHX as part of cord care for all newborns. The project supported enhanced postnatal care through several interventions: postnatal education during antenatal care for new parents; improved pre-discharge examinations and education on danger signs for mother and babies; the provision of CHX gel for cord care for all babies; and, in the rural catchment areas of two selected health facilities, the provision of home visits by village health volunteers to new mothers before and after delivery. The outcomes from the study supported the feasibility and acceptability of an enhanced postnatal care package, including the use of CHX gel for umbilical cord care in several different settings in PNG.

The Burnet PNG project addressed two needs: the dissemination of information and educational tools relating to the postnatal period and implementation research into how to best introduce CHX as part of cord care for all newborns.

Continued scale-up in Kenya throughout 2020

The GSK/STC programme in Kenya has adopted multiple lines of activity to support the development of an underpinning architecture and a practical environment for scaling up CHX by working in close collaboration with the MoH, regulatory bodies and NGOs, such as Amref, PATH and Nutrition International.

This included supporting the MoH in the creation of **a national scale-up plan**, collaborating with Amref in the development of policy briefs and information and educational materials for healthcare workers and communities, and advocating and driving the integration of CHX indicators within the Kenya Health Information System, which was crucial for tracking CHX coverage and enabling accountability.

STC has also focused its **operational work in 17 counties** to support the strategic planning, training, and safe implementation of CHX into practice, complementing initiatives of the MoH and NGOs in other counties.

As of January 2021, CHX is now available in all counties in Kenya and **43% of all newborns on average receive the protection of CHX**. Coverage rates in the counties supported by the GSK/STC programme are higher than the average (up to 77%) with 7 of the 10 highest performing counties being supported by the programme. Overall, a strong footprint is now in place nationally from which to build upwards.

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Conclusions

Innovative partnerships and conducive environmental factors are required for pharmaceutical companies to develop and deliver essential medicines sustainably to LMICs. Involvement of a global organization may bring added value to both increase the visibility of the unmet need and also encourage the participation of other players. GSK used its prior expertise and data to expedite regulatory approval of a reformulated CHX gel specifically for LMICs, partnering with STC to support its introduction in Kenya, including via a MAP.

Working in partnership was fundamental to enable access to essential medicines for the people who need them most, and successful product development was only the first step in a long, complex journey. For all the commitment, adaptation and social investment GSK demonstrated in developing CHX gel, in Kenya, it was the continued collaboration with STC and the facilitation by, and commitment of, national- and county-level MoHs that enabled the uptake of CHX gel. CHX currently has an increasing footprint in routine care in all counties and a solidified position in the healthcare system, such that the aim of enabling all vulnerable newborns in Kenya to benefit from its protection in the future is now a realistic possibility.

Global policy and WHO recommendations are important in supporting increased access to healthcare; however, policies do not always translate into implementation at a country level. Awareness and demand-generation activities are critical in moving global health policy towards country implementation and uptake. Increasing access to healthcare is an achievable development goal and requires strong collaboration between the private and public sectors. To facilitate sustainable development, manufacture, supply, scale-up and access to essential medicines in LMICs, pharmaceutical companies, funders, governments, NGOs and others each bring unique expertise to help drive innovation, collaboration and share learning, but also share risks. Through the sustainability of global health R&D and subsequent access through such partnerships, the chances of realising the UN SDGs by 2030 can be enhanced.

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Abbreviations

AE:	adverse event
ATM:	access to medicines
CHX:	chlorhexidine
CWG:	Chlorhexidine Working Group
DCC:	dry cord care
EMA:	European Medicines Agency
EML:	essential medicines list
I-NGO:	international non-governmental organisation
KEMSA:	Kenya Medical Supplies Authority
LMIC:	low- and middle-income country
MAP:	Managed Access Programme
MoH:	Ministry of Health
MoHP:	Ministry of Health and Population
PNG:	Papua New Guinea
R&D:	research and development
SDG:	Sustainable Development Goal
STC:	Save the Children
UHC:	universal health coverage
UN:	United Nations
USAID:	United States Agency for International Development
USP:	United States Pharmacopeia
WHO:	World Health Organization

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