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Increasing access to essential medicines through partnership: experience in developing and delivering chlorhexidine gel for newborn cord care

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CHX Review article March 2022

Increasing access to essential medicines through partnership: experience in developing and delivering chlorhexidine gel for newborn cord care

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ABSTRACT (149/300)

Sustainable access to essential medicines in low- and middle-income countries requires innovative cross-sectoral collaboration throughout the lifecycle of a medicine. Partnerships are essential to address the systemic challenges of global health and health inequity. Pharmaceutical companies, funders, governments, international non-governmental organisations (I-NGOs) and other key stakeholders can leverage, through effective partnership working, their unique expertise to help drive innovation and share learnings and risks. Here we reflect on one approach taken in the development and supply of chlorhexidine digluconate 7.1% w/w gel (equivalent to 4% w/w chlorhexidine) for neonatal cord care. We describe and analyse the steps taken by GlaxoSmithKline to increase access to chlorhexidine gel, including partnering with the I-NGO Save the Children in Western Kenya. Learning points gained along 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.

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KEY MESSAGES

- Barriers to medicine access in low-resource settings are common; to address this, effective partnerships are required. Here we describe learnings from a multisectoral collaboration to develop and supply chlorhexidine gel for neonatal cord care in Western Kenya.
- Insights and learnings from service users and context-based development partners are critical throughout a product's lifecycle to optimise suitability and acceptability.
- Manufacturing processes should be simple to enable transfer to local manufacturers but may fail without proactive engagement strategies to stimulate demand and interest.
- Sustainable side-effect reporting/pharmacovigilance is essential when introducing a new medicine in resource-limited settings where side-effect-reporting mechanisms may not be robust.
- Integrating new commodities is complex. Governmental commitment and actions to improve service supply, stimulate demand and sustain community-level engagement, creates better conditions for adoption.

Keywords (1–5): Public health; Neonatal health; Health policy; Health education and promotion; Prevention strategies

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INTRODUCTION

The World Health Organization (WHO) defines essential medicines as those that "satisfy the priority health care needs of the population".[1] As such, they are crucial for saving lives, promoting health and achieving sustainable development: they must be both available and affordable, in appropriate dosages and with assured quality.[2] However, access to essential medicines in low- and middle-income countries (LMICs) remains a significant problem, and such countries face numerous barriers to access.

PARTNERSHIPS TO ADDRESS BARRIERS TO MEDICINES ACCESS

The scale, potential and contribution of the private sector towards the United Nations (UN) Sustainable Development Goal (SDG) 3 (Good Health and Well-Being) to achieve universal health coverage and overcome obstacles for accessing essential medicines in LMICs has been an important and recurring focus of discussion.[3] Innovative cross-sectoral partnerships may leverage the complementary expertise of different partners to ensure sustainability of access while also helping to share risk. Here we reflect upon a partnership between GlaxoSmithKline (GSK), Save the Children (STC) and other stakeholders to increase access to chlorhexidine digluconate 7.1% (CHX) gel (included in the WHO list of essential medicines) for neonatal cord care in Western Kenya. Lessons learned from this partnership and a Managed Access Programme (MAP) are shared, with the aim of making key recommendations that may be of relevance for similar projects in the future. For the interested reader, a more detailed summary of learnings can be found here: https://www.savethechildren.org.uk/content/dam/gb/reports/umbipro-lessons-learned-document.pdf. **Figure 1** summarises key steps in the programme.

NEWBORN CORD CARE IN LMICs

Newborns in LMICs – where births commonly occur at home without trained healthcare workers – are susceptible to infection, with the newly cut umbilical cord representing a frequent bacterial entry point.[4] To address this need, the WHO recommends application of CHX in settings with high

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neonatal mortality rates (>30 deaths/1,000 live births) or to replace harmful traditional cord care substances.[5] This followed successful development, field-trialling and scale-up of CHX gel in South Asia, most notably in Nepal.[6] The UN estimated that if high-quality affordable CHX was supplied to 50 resource-limited countries, 422,000 neonatal lives could be saved over a 5-year period.[7]

ENHANCING ACCESS TO CHX FOR NEWBORN CORD CARE IN KENYA THROUGH A PUBLIC-PRIVATE PARTNERSHIP

In 2012, in response to these needs, GSK set out to develop a not-for-profit, quality assured gel formulation of 7.1% CHX (equivalent to 4% w/w CHX) suitable for use in resource-limited countries that could pass stringent regulatory review. With access in mind, the formulation was kept as simple as possible to enable local manufacturers to produce an identical product to both increase global CHX supply and enable a sustainable supply. In 2016, following an accelerated review, GSK's CHX gel was granted a positive opinion by the European Medicines Agency (EMA) which supported national registrations (**Figure 1).**

In Kenya, neonatal mortality contributes to over 40% of child deaths,[8] with infection a leading cause.[9] Although the national neonatal mortality rate in Kenya is below the WHO threshold for recommending CHX, wide regional disparities exist with high levels of home deliveries and harmful traditional cord-care practices in some regions. Following a request from the Kenyan Ministry of Health (MoH) for early access to CHX gel in preparation for national scale-up, GSK worked closely with STC, who partnered with the Bungoma County Department of Health to implement a MAP and facilitated collection of insights on user experiences and practices. The MAP provided opportunities to understand acceptability of CHX gel among healthcare providers and mothers, examine factors influencing provision and uptake, and determine acceptability of information, education and communication materials.[10, 11] In parallel, the Kenyan MoH led development and dissemination of national guidelines and updated the Kenya essential medicines list to include CHX.

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STC, Amref Health Africa and the Kenyan MoH (Division of Neonatal and Child Health), with engagement from the County First Ladies Association[12], subsequently partnered to perform advocacy and sensitisation work. This led to the development of national guidelines, healthcare worker 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.[13] Crucially, STC and the other partners fostered sustained community engagement, which was key to building trust and overcoming deep-rooted cultural practices about cord care among families and healthcare workers.

At a county level, local advocacy led Bungoma and another county, Busia, to incorporate CHX for cord care into their county-specific guidelines and ensured funds were secured to support routine procurement of locally manufactured CHX through the national supply chain system, thereby encouraging sustainability. Additionally, a pharmacovigilance training model, jointly disseminated by GSK and STC, successfully generated short-term safety information for CHX gel during the MAP, which complemented the well-established safety profile of CHX products.

In order to facilitate the transfer of technical and quality know-how to multiple local manufacturers, an agreement with United States Pharmacopeia (USP) through the Promoting the Quality of Medicines programme funded by the United States Agency for International Development (USAID)[14], was established. This 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.

LESSONS LEARNED

Innovation and partnership working have characterised the development and distribution of CHX gel in LMICs from the outset. Established in 2014, the CHX Working Group (CWG) – comprising manufacturers, international non-governmental organisations (I-NGOs), universities and governments – was convened by the non-profit organisation PATH to advance the use of CHX

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through advocacy and technical assistance. Insights from CWG members contributed to the decision to package CHX gel in single-dose sachets to facilitate ease of use and optimal dose application to avoid retention of excess gel for alternative uses, and inclusion of pictorial instructions to reinforce appropriate use in low literacy settings.

Generating these insights as early as possible is recommended; however, it is also important to continue to gather information throughout the lifecycle of the medicine during and after the development pathway and adapt accordingly. For example, reports of other chlorhexidine solutions and gel products being mistaken for eye treatments and causing irreversible eye-injury, including blindness, reinforced the importance of suitable packaging, labelling and appropriate warnings.[15]

The formulation and manufacturing process for CHX gel was developed to be as simple as possible while adhering to high quality standards, with control strategies in place to minimise formation of impurities, in particular the potential human carcinogen 4-chloroaniline.[16] It was essential the manufacturing process was easily transferable to local manufacturers without compromising quality. Working with an organisation like United States Pharmacopoeia can greatly facilitate the transfer of technical and quality know-how to multiple local manufacturers, allowing efficient resource use and enhancing sustainability, while complying with quality standards. However, even with technical transfer details freely available[17], a simple manufacturing process may not be sufficient, and thus additional proactive strategies may be required to engage with local manufacturers to stimulate demand and interest in new products.

The regulatory environment is also highly complex and can be challenging. Although a fast-track positive opinion of CHX gel was achieved under the EMA's Article 58 process[18], in some instances national registrations took in excess of 2 years. Humanitarian organisations are often the primary procurers of essential medicines in LMICs, adhering to strict quality standards for the medicines they procure. Generally, this requires a product to be approved by a stringent regulatory authority or

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adherence to the WHO prequalification process. Thus, greater alignment between the EMA and WHO may hasten access to other essential medicines in LMICs.

As more medicines are developed in response to diseases common to resource-limited settings, sustainable pharmacovigilance is a concern. A low-intervention pharmacovigilance training model was jointly and successfully disseminated by GSK and STC in Kenya; however, further improvements in underlying healthcare systems and new multi-stakeholder initiatives, such as the WHO Project 3-S[19], may enable local stakeholders to play a greater role in long-term safety monitoring in the future.

Despite high user acceptability, a relatively supportive policy environment and availability of locally manufactured product in Kenya, CHX products still fail to reach some newborns who would benefit most, as a consequence of policies that inadvertently prevent CHX from easily reaching babies born at home where impact on infection might be greatest. This highlights the importance of ensuring that healthcare policies are not in conflict but promote equitable approaches to context-based public health procurement and access to interventions that strengthen the effectiveness and reach of maternal and neonatal care.

Two randomised controlled trials of chlorhexidine in sub-Saharan Africa (Tanzania and Zambia)[20, 21] failed to show efficacy of CHX in reducing neonatal mortality, although one study did demonstrate significantly reduced rates of omphalitis (cord infection) following CHX use. However, in both studies, all participants were encouraged to keep umbilical cords clean and dry. These improved cord-care practices are likely to have led to lower mortality in both the CHX and control groups, emphasising that decisions on targeted CHX roll-out should be considered in the context of other educational and healthcare provision practices in that region.

Evidence of efficacy and safety is crucial to maintain confidence in any product. The aforementioned WHO safety alert relating to errors in administration reinforced the need for education and training on appropriate use and the importance of differential packaging of the product and patient

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information. However, the safety alert, taken together with data from the two previously described clinical trials in sub-Saharan Africa[20, 21], is likely to 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.

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. A top-down approach from government may be insufficient for a product to be adopted and accepted. Trusted field partners can work effectively with the spectrum of stakeholder groups to ensure the context and perspectives of community users and other actors are represented and accounted for. Changing knowledge, attitudes and practices is required at all levels. A combined approach to improve service supply and demand (e.g. provision of training for healthcare workers and local campaigns to raise awareness among mothers) and sustained community-level engagement, creates better conditions for a product to be successfully adopted and accepted.

The uptake of CHX products for cord care has been slow in high-need countries due to many factors, including lack of awareness and demand from end users, 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 many other countries, sometimes necessitating difficult procurement choices to be made, even between medicines that are deemed essential. Locally manufactured CHX has helped to increase access in Kenya but there remains a need for continuous, sustained long-term effort to ensure uptake of essential medicines such as CHX.

CONCLUSIONS

Innovative partnerships are required throughout the lifecycle of a new intervention to ensure sustainable access to essential medicines in LMICs. Pharmaceutical companies, funders, governments, I-NGOs and other key stakeholders need to integrate their unique expertise to inform the design and implementation stages. For example, market awareness and community sensitization

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initiated in parallel to product development and regulatory harmonization would accelerate availability and uptake. Ongoing partnerships with in-country stakeholders would enable continued learnings and optimization. Through this, realisation of the UN's SDG of achieving universal health coverage, and a world where all people have equitable access to quality, essential healthcare without risk of financial hardship by 2030, can be greatly enhanced.

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COMPETING INTERESTS

EDA, RG are employees of GSK. EDA, RG and PW hold stocks/shares in GSK. AC and KK are employed by Save the Children, UK.

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Patients or the public were not involved with the conception or development of this review article.

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Figure 1. Increasing access to essential medicines through partnership: the journey of chlorhexidine.

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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

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

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)

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

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ABSTRACT (149/300)

Sustainable access to essential medicines in low- and middle-income countries requires innovative cross-sectoral collaboration throughout the lifecycle of a medicine. Partnerships are essential to address the systemic challenges of global health and health inequity. Pharmaceutical companies, funders, governments, international non-governmental organisations (I-NGOs) and other key stakeholders can leverage, through effective partnership working, their unique expertise to help drive innovation and share learnings and risks. Here we reflect on one approach taken in the development and supply of chlorhexidine digluconate 7.1% w/w gel (equivalent to 4% w/w chlorhexidine) for neonatal cord care. We describe and analyse the steps taken by GSK to increase access to chlorhexidine gel, including partnering with the I-NGO Save the Children in Western Kenya. Learning points gained along 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.

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KEY MESSAGES

- Barriers to medicine access in low-resource settings are common; to address this, effective partnerships are required. Here we describe learnings from a multisectoral collaboration to develop and supply chlorhexidine gel for neonatal cord care in Western Kenya.
- Insights and learnings from service users and context-based development partners are critical throughout a product's lifecycle to optimise suitability and acceptability.
- Manufacturing processes should be simple to enable transfer to local manufacturers but may fail without proactive engagement strategies to stimulate demand and interest.
- Sustainable side-effect reporting/pharmacovigilance is essential when introducing a new medicine in resource-limited settings where side-effect-reporting mechanisms may not be robust.
- Integrating new commodities is complex. Governmental commitment and actions to improve service supply, stimulate demand and sustain community-level engagement, creates better conditions for adoption.

Keywords (1–5): Public health; Neonatal health; Health policy; Health education and promotion; Prevention strategies

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INTRODUCTION

The World Health Organization (WHO) defines essential medicines as those that "satisfy the priority health care needs of the population".[1] As such, they are crucial for saving lives, promoting health and achieving sustainable development: they must be both available and affordable, in appropriate dosages and with assured quality.[2] However, access to essential medicines in low- and middle-income countries (LMICs) remains a significant problem, and such countries face numerous barriers to access.

PARTNERSHIPS TO ADDRESS BARRIERS TO MEDICINES ACCESS

The scale, potential and contribution of the private sector towards the United Nations (UN) Sustainable Development Goal (SDG) 3 (Good Health and Well-Being) to achieve universal health coverage and overcome obstacles for accessing essential medicines in LMICs has been an important and recurring focus of discussion.[3] Innovative cross-sectoral partnerships may leverage the complementary expertise of different partners to ensure sustainability of access while also helping to share risk. Here we reflect upon a partnership between GSK, Save the Children (STC) and other stakeholders to increase access to chlorhexidine digluconate 7.1% (CHX) gel (included in the WHO list of essential medicines) for neonatal cord care in Western Kenya. Lessons learned from this partnership and a Managed Access Programme (MAP) are shared, with the aim of making key recommendations that may be of relevance for similar projects in the future. For the interested reader, a more detailed summary of learnings can be found here: https://www.savethechildren.org.uk/content/dam/gb/reports/umbipro-lessons-learned-document.pdf. **Figure 1** summarises key steps in the programme.[4]

NEWBORN CORD CARE IN LMICs

In 2018, an estimated 15% of all neonatal deaths globally were due to sepsis, with the overall highest incidence in low-income countries.[5] Newborns in LMICs – where births commonly occur at home without trained healthcare workers – are susceptible to infection, with the newly cut umbilical

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cord representing a frequent bacterial entry point.[6] The efficacy of CHX 7.1% solution for the prevention of umbilical cord infection was demonstrated by three community-based randomised controlled trials in South Asia.[7,8,9] WHO recommends the use of CHX in settings with high neonatal mortality rates (>30 deaths/1,000 live births) or to replace harmful traditional cord care substances.[10] This followed successful development, field-trialling and scale-up of CHX gel in South Asia, most notably in Nepal.[11] The UN estimated that if high-quality affordable CHX was supplied to 50 resource-limited countries, 422,000 neonatal lives could be saved over a 5-year period.[12]

ENHANCING ACCESS TO CHX FOR NEWBORN CORD CARE IN KENYA THROUGH A PUBLIC-PRIVATE PARTNERSHIP

In 2012, in response to these needs, GSK set out to develop a not-for-profit, quality assured gel formulation of chlorhexidine digluconate 7.1% w/w gel (equivalent to 4% w/w chlorhexidine) - referred to as CHX suitable for use in resource-limited countries that could pass stringent regulatory review. Insights gathered during development suggested that a gel rather than a liquid formulation would increase ease of use. With access in mind, the formulation was kept as simple as possible to enable local manufacturers to produce an identical product to both increase global CHX supply and enable a sustainable supply. In 2016, following an accelerated review, GSK's CHX gel was granted a positive opinion by the European Medicines Agency (EMA) which supported national registrations **(Figure 1)**.[4]

In Kenya, neonatal mortality contributes to over 40% of child deaths,[13] with infection a leading cause.[14] Although the national neonatal mortality rate in Kenya is below the WHO threshold for recommending CHX, wide regional disparities exist with high levels of home deliveries and harmful traditional cord-care practices in some regions. Following a request from the Kenyan Ministry of Health (MoH) for early access to CHX gel in preparation for national scale-up, GSK worked closely with STC, who partnered with the Bungoma County Department of Health to implement a MAP and facilitated collection of insights on user experiences and practices. The MAP provided opportunities

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to understand acceptability of CHX gel among healthcare providers and mothers, examine factors influencing provision and uptake, and determine acceptability of information, education and communication materials.[15, 16] In parallel, the Kenyan MoH led development and dissemination of national guidelines and updated the Kenya essential medicines list to include CHX.

STC, Amref Health Africa and the Kenyan MoH (Division of Neonatal and Child Health), with engagement from the County First Ladies Association,[17] subsequently partnered to perform advocacy and sensitisation work. This led to the development of national guidelines, healthcare worker 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.[18] Crucially, STC and the other partners fostered sustained community engagement, which was key to building trust and overcoming deep-rooted cultural practices about cord care among families and healthcare workers.

At a county level, local advocacy led Bungoma and another county, Busia, to incorporate CHX for cord care into their county-specific guidelines and ensured funds were secured to support routine procurement of locally manufactured CHX through the national supply chain system, thereby encouraging sustainability. Additionally, a pharmacovigilance training model, jointly disseminated by GSK and STC, successfully generated short-term safety information for CHX gel during the MAP, which complemented the well-established safety profile of CHX products.

In order to facilitate the transfer of technical and quality know-how to multiple local manufacturers, an agreement with United States Pharmacopeia (USP) through the Promoting the Quality of Medicines programme funded by the United States Agency for International Development,[19] was established. This 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.

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LESSONS LEARNED

Innovation and partnership working have characterised the development and distribution of CHX gel in LMICs from the outset. Established in 2014, the CHX Working Group (CWG) – comprising manufacturers, international non-governmental organisations (I-NGOs), universities and governments – was convened by the non-profit organisation PATH to advance the use of CHX through advocacy and technical assistance. Insights from CWG members contributed to the decision to package CHX gel in single-dose sachets to facilitate ease of use and optimal dose application to avoid retention of excess gel for alternative uses, and inclusion of pictorial instructions to reinforce appropriate use in low literacy settings.

Generating these insights as early as possible is recommended; however, it is also important to continue to gather information throughout the lifecycle of the medicine during and after the development pathway and adapt accordingly. For example, reports of other chlorhexidine solutions and gel products being mistaken for eye treatments and causing irreversible eye-injury, including blindness, reinforced the importance of suitable packaging, labelling and appropriate warnings, as detailed in the 2015 WHO Alert.[20]

The formulation and manufacturing process for CHX gel was developed to be as simple as possible while adhering to high quality standards, with control strategies in place to minimise formation of impurities, in particular the potential human carcinogen 4-chloroaniline.[21] It was essential the manufacturing process was easily transferable to local manufacturers without compromising quality. Working with an organisation like USP can greatly facilitate the transfer of technical and quality know-how to multiple local manufacturers, allowing efficient resource use and enhancing sustainability, while complying with quality standards. However, even with technical transfer details freely available,[22] a simple manufacturing process may not be sufficient, and thus additional proactive strategies may be required to engage with local manufacturers to stimulate demand and interest in new products.

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The regulatory environment is also highly complex and can be challenging. Although a fast-track positive opinion of CHX gel was achieved under the EMA's Article 58 process,[23] in some instances national registrations took in excess of 2 years. Humanitarian organisations are often the primary procurers of essential medicines in LMICs, adhering to strict quality standards for the medicines they procure. Generally, this requires a product to be approved by a stringent regulatory authority or adherence to the WHO prequalification process. Thus, greater alignment between the EMA and WHO may hasten access to other essential medicines in LMICs.

As more medicines are developed in response to diseases common to resource-limited settings, sustainable pharmacovigilance is a concern. A low-intervention pharmacovigilance training model was jointly and successfully disseminated by GSK and STC in Kenya; however, further improvements in underlying healthcare systems and new multi-stakeholder initiatives, such as the WHO Project 3-S,[24] may enable local stakeholders to play a greater role in long-term safety monitoring in the future.

Despite high user acceptability, a relatively supportive policy environment and availability of locally manufactured product in Kenya, CHX products still fail to reach some newborns who would benefit most, as a consequence of policies that inadvertently prevent CHX from easily reaching babies born at home where impact on infection might be greatest. This highlights the importance of ensuring that healthcare policies are not in conflict but promote equitable approaches to context-based public health procurement and access to interventions that strengthen the effectiveness and reach of maternal and neonatal care.

Two randomised controlled trials of chlorhexidine in sub-Saharan Africa (Tanzania and Zambia)[25, 26] failed to show efficacy of CHX in reducing neonatal mortality, although one study did demonstrate significantly reduced rates of omphalitis (cord infection) following CHX use. Participants in both studies were encouraged to keep umbilical cords clean and dry which is likely to have led to lower mortality in both the CHX and control groups. Aligned to the recently updated WHO

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Guidelines,[27] decisions on targeted CHX roll-out should be considered in the context of other educational and healthcare provision practices in that region, and prevalence of harmful substance application on cords.

Evidence of efficacy and safety is crucial to maintain confidence in any product. The aforementioned WHO safety alert relating to errors in administration reinforced the need for education and training on appropriate use and the importance of differential packaging of the product and patient information. However, the safety alert, taken together with data from the two previously described clinical trials in sub-Saharan Africa,[25, 26] is likely to 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.

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. A top-down approach from government may be insufficient for a product to be adopted and accepted. Trusted field partners can work effectively with the spectrum of stakeholder groups to ensure the context and perspectives of community users and other actors are represented and accounted for. Changing knowledge, attitudes and practices is required at all levels. A combined approach to improve service supply and demand (e.g. provision of training for healthcare workers and local campaigns to raise awareness among mothers) and sustained community-level engagement, creates better conditions for a product to be successfully adopted and accepted.

The uptake of CHX products for cord care has been slow in high-need countries due to many factors, including lack of awareness and demand from end users, 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 many other countries, sometimes necessitating difficult procurement choices to be made, even between medicines that are deemed essential.

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Locally manufactured CHX has helped to increase access in Kenya but there remains a need for continuous, sustained long-term effort to ensure uptake of essential medicines such as CHX.

CONCLUSIONS

Innovative partnerships are required throughout the lifecycle of a new intervention to ensure sustainable access to essential medicines in LMICs. Pharmaceutical companies, funders, governments, I-NGOs and other key stakeholders need to integrate their unique expertise to inform the design and implementation stages. For example, market awareness and community sensitization initiated in parallel to product development and regulatory harmonization would accelerate availability and uptake. Ongoing partnerships with in-country stakeholders would enable continued learnings and optimization. Through this, realisation of the UN's SDG of achieving universal health coverage, and a world where all people have equitable access to quality, essential healthcare without risk of financial hardship by 2030, can be greatly enhanced.

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CONTRIBUTORS

All listed authors contributed substantially to the planning and implementation of work described in this practice report. All authors revised the manuscript critically for important intellectual content and approved the final version for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately answered and resolved.

COMPETING INTERESTS

EDA, RG are employees of the GSK group of companies. EDA, RG and PW hold stocks/shares in the GSK group of companies. AC and KK are employed by Save the Children, UK.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

Patients or the public were not involved with the conception or development of this review article.

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Figure 1. Increasing access to essential medicines through partnership: the journey of chlorhexidine.[4]

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Increasing access to essential medicines through partnership

The journey of chlorhexidine

gsk | Save the Children
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

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

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)

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

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Increasing access to essential medicines through partnership: experience in developing and delivering chlorhexidine gel for newborn cord care

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ABSTRACT (149/300)

Sustainable access to essential medicines in low- and middle-income countries requires innovative cross-sectoral collaboration throughout the lifecycle of a medicine. Partnerships are essential to address the systemic challenges of global health and health inequity. Pharmaceutical companies, funders, governments, international non-governmental organisations (I-NGOs) and other key stakeholders can leverage, through effective partnership working, their unique expertise to help drive innovation and share learnings and risks. Here we reflect on one approach taken in the development and supply of chlorhexidine digluconate 7.1% w/w gel (equivalent to 4% w/w chlorhexidine) for neonatal cord care. We describe and analyse the steps taken by ~~GlaxoSmithKline~~GSK to increase access to chlorhexidine gel, including partnering with the I-NGO Save the Children in Western Kenya. Learning points gained along 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.

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KEY MESSAGES

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INTRODUCTION

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ENHANCING ACCESS TO CHX FOR NEWBORN CORD CARE IN KENYA THROUGH A PUBLIC-PRIVATE PARTNERSHIP

In 2012, in response to these needs, GSK set out to develop a not-for-profit, quality assured gel formulation of chlorhexidine digluconate 7.1% ~~CHX~~w/w gel (equivalent to 4% w/w ~~CHX)~~chlorhexidine) - referred to as CHX suitable for use in resource-limited countries that could pass stringent regulatory review. Insights gathered during development suggested that a gel rather than a liquid formulation would increase ease of use. With access in mind, the formulation was kept as simple as possible to enable local manufacturers to produce an identical product to both increase global CHX supply and enable a sustainable supply. In 2016, following an accelerated review, GSK's CHX gel was granted a positive opinion by the European Medicines Agency (EMA) which supported national registrations **(Figure 1~~).~~)**.[4]

In Kenya, neonatal mortality contributes to over 40% of child deaths,[~~8~~13] with infection a leading cause.[~~9~~14] Although the national neonatal mortality rate in Kenya is below the WHO threshold for recommending CHX, wide regional disparities exist with high levels of home deliveries and harmful traditional cord-care practices in some regions. Following a request from the Kenyan Ministry of Health (MoH) for early access to CHX gel in preparation for national scale-up, GSK worked closely with STC, who partnered with the Bungoma County Department of Health to implement a MAP and

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facilitated collection of insights on user experiences and practices. The MAP provided opportunities to understand acceptability of CHX gel among healthcare providers and mothers, examine factors influencing provision and uptake, and determine acceptability of information, education and communication materials.[~~10, 11~~15, 16] In parallel, the Kenyan MoH led development and dissemination of national guidelines and updated the Kenya essential medicines list to include CHX.

STC, Amref Health Africa and the Kenyan MoH (Division of Neonatal and Child Health), with engagement from the County First Ladies Association,[1~~2~~7]~~,~~ subsequently partnered to perform advocacy and sensitisation work. This led to the development of national guidelines, healthcare worker 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.[~~13~~18] Crucially, STC and the other partners fostered sustained community engagement, which was key to building trust and overcoming deep-rooted cultural practices about cord care among families and healthcare workers.

At a county level, local advocacy led Bungoma and another county, Busia, to incorporate CHX for cord care into their county-specific guidelines and ensured funds were secured to support routine procurement of locally manufactured CHX through the national supply chain system, thereby encouraging sustainability. Additionally, a pharmacovigilance training model, jointly disseminated by GSK and STC, successfully generated short-term safety information for CHX gel during the MAP, which complemented the well-established safety profile of CHX products.

In order to facilitate the transfer of technical and quality know-how to multiple local manufacturers, an agreement with United States Pharmacopeia (USP) through the Promoting the Quality of Medicines programme funded by the United States Agency for International Development ~~(USAID)[14],~~[19] was established.~~-~~ This 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.

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LESSONS LEARNED

Innovation and partnership working have characterised the development and distribution of CHX gel in LMICs from the outset. Established in 2014, the CHX Working Group (CWG) – comprising manufacturers, international non-governmental organisations (I-NGOs), universities and governments – was convened by the non-profit organisation PATH to advance the use of CHX through advocacy and technical assistance. Insights from CWG members contributed to the decision to package CHX gel in single-dose sachets to facilitate ease of use and optimal dose application to avoid retention of excess gel for alternative uses, and inclusion of pictorial instructions to reinforce appropriate use in low literacy settings.

Generating these insights as early as possible is recommended; however, it is also important to continue to gather information throughout the lifecycle of the medicine during and after the development pathway and adapt accordingly. For example, reports of other chlorhexidine solutions and gel products being mistaken for eye treatments and causing irreversible eye-injury, including blindness, reinforced the importance of suitable packaging, labelling and appropriate warnings~~.[15,~~ as detailed in the 2015 WHO Alert.[20]

The formulation and manufacturing process for CHX gel was developed to be as simple as possible while adhering to high quality standards, with control strategies in place to minimise formation of impurities, in particular the potential human carcinogen 4-chloroaniline.[~~16~~21] It was essential the manufacturing process was easily transferable to local manufacturers without compromising quality. Working with an organisation like ~~United States Pharmacopoeia~~USP can greatly facilitate the transfer of technical and quality know-how to multiple local manufacturers, allowing efficient resource use and enhancing sustainability, while complying with quality standards. However, even with technical transfer details freely available~~[17],~~[22] a simple manufacturing process may not be sufficient, and thus additional proactive strategies may be required to engage with local manufacturers to stimulate demand and interest in new products.

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The regulatory environment is also highly complex and can be challenging. Although a fast-track positive opinion of CHX gel was achieved under the EMA's Article 58 process~~[18],~~[23] in some instances national registrations took in excess of 2 years. Humanitarian organisations are often the primary procurers of essential medicines in LMICs, adhering to strict quality standards for the medicines they procure. Generally, this requires a product to be approved by a stringent regulatory authority or adherence to the WHO prequalification process. Thus, greater alignment between the EMA and WHO may hasten access to other essential medicines in LMICs.

As more medicines are developed in response to diseases common to resource-limited settings, sustainable pharmacovigilance is a concern. A low-intervention pharmacovigilance training model was jointly and successfully disseminated by GSK and STC in Kenya; however, further improvements in underlying healthcare systems and new multi-stakeholder initiatives, such as the WHO Project 3-S~~[19],~~[24] may enable local stakeholders to play a greater role in long-term safety monitoring in the future.

Despite high user acceptability, a relatively supportive policy environment and availability of locally manufactured product in Kenya, CHX products still fail to reach some newborns who would benefit most, as a consequence of policies that inadvertently prevent CHX from easily reaching babies born at home where impact on infection might be greatest. This highlights the importance of ensuring that healthcare policies are not in conflict but promote equitable approaches to context-based public health procurement and access to interventions that strengthen the effectiveness and reach of maternal and neonatal care.

Two randomised controlled trials of chlorhexidine in sub-Saharan Africa (Tanzania and Zambia)[~~20,~~ ~~21~~25, 26] failed to show efficacy of CHX in reducing neonatal mortality, although one study did demonstrate significantly reduced rates of omphalitis (cord infection) following CHX use. ~~However,~~Participants in both studies~~, all participants~~ were encouraged to keep umbilical cords clean and dry~~. These improved cord care practices are~~ which is likely to have led to lower mortality in both

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the CHX and control groups~~, emphasising that~~. Aligned to the recently updated WHO Guidelines,[27] decisions on targeted CHX roll-out should be considered in the context of other educational and healthcare provision practices in that region, and prevalence of harmful substance application on cords.

Evidence of efficacy and safety is crucial to maintain confidence in any product. The aforementioned WHO safety alert relating to errors in administration reinforced the need for education and training on appropriate use and the importance of differential packaging of the product and patient information. However, the safety alert, taken together with data from the two previously described clinical trials in sub-Saharan Africa~~[20, 21],~~,[25, 26] is likely to 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.

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. A top-down approach from government may be insufficient for a product to be adopted and accepted. Trusted field partners can work effectively with the spectrum of stakeholder groups to ensure the context and perspectives of community users and other actors are represented and accounted for. Changing knowledge, attitudes and practices is required at all levels. A combined approach to improve service supply and demand (e.g. provision of training for healthcare workers and local campaigns to raise awareness among mothers) and sustained community-level engagement, creates better conditions for a product to be successfully adopted and accepted.

The uptake of CHX products for cord care has been slow in high-need countries due to many factors, including lack of awareness and demand from end users, 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 many other countries, sometimes necessitating difficult procurement choices to be made, even between medicines that are deemed essential.

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Locally manufactured CHX has helped to increase access in Kenya but there remains a need for continuous, sustained long-term effort to ensure uptake of essential medicines such as CHX.

CONCLUSIONS

Innovative partnerships are required throughout the lifecycle of a new intervention to ensure sustainable access to essential medicines in LMICs. Pharmaceutical companies, funders, governments, I-NGOs and other key stakeholders need to integrate their unique expertise to inform the design and implementation stages. For example, market awareness and community sensitization initiated in parallel to product development and regulatory harmonization would accelerate availability and uptake. Ongoing partnerships with in-country stakeholders would enable continued learnings and optimization. Through this, realisation of the UN's SDG of achieving universal health coverage, and a world where all people have equitable access to quality, essential healthcare without risk of financial hardship by 2030, can be greatly enhanced.

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COMPETING INTERESTS

EDA, RG are employees of the GSK group of companies. EDA, RG and PW hold stocks/shares in the GSK group of companies. AC and KK are employed by Save the Children, UK.

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Figure 1. Increasing access to essential medicines through partnership: the journey of chlorhexidine. [4]

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