From Research to Use

Saving Newborn Lives With Chlorhexidine for Umbilical Cord Care
Roughly 2.76 million newborns die globally each year, and infections cause at least 15% of those deaths. A baby’s recently cut umbilical cord can be an entry point for bacteria that can cause life-threatening newborn sepsis. Optimal cord care at birth and in the first week of life, especially in settings with poor hygiene, is critical to averting neonatal deaths.

Chlorhexidine digluconate in low concentrations has long been a low-cost antiseptic widely used for hand sanitizers, mouth wash, and preoperative skin preparation. Its novel formulation for umbilical cord care, 7.1% chlorhexidine digluconate (CHX), has a higher concentration of active ingredient than other currently marketed products and can prevent cord infection and neonatal sepsis. Over the past decade, CHX has moved rapidly from initial concept to a global health success. Today, CHX is implemented as part of the package of essential newborn interventions in more than ten countries in South Asia and sub-Saharan Africa (Bangladesh, Democratic Republic of the Congo [DRC], Ethiopia, Kenya, Liberia, Madagascar, Malawi, Mozambique, Nepal, Nigeria, Pakistan, Sierra Leone) and will save many newborn lives in the years to come.

The story of chlorhexidine is a story of a product’s journey from evidence building to policy development, production, and demand generation—and eventually to adoption and scale-up. It is also the story of the many groups and individuals who have committed to identifying and scaling an effective, appropriate intervention to improve newborn health and protect babies from preventable illnesses. This report showcases the scope and breadth of the work of these groups and individuals over the years to ensure that CHX is widely adopted to save newborn lives.
The trajectory from research to use

**2002**
- Cluster-randomized community-based controlled trial to evaluate impact of CHX on omphalitis and neonatal mortality: NEPAL

**2005**
- USAID and NICHD meeting to review evidence of CHX on infection prevention

**2007**
- Cluster-randomized community-based controlled trial to evaluate impact of umbilical cord cleansing with CHX on neonatal mortality and omphalitis: BANGLADESH

**2008**
- Cluster-randomized community-based controlled trial to evaluate impact of CHX on omphalitis and neonatal mortality: PAKISTAN

**2009**
- Randomized noninferiority trial: CHX gel vs. aqueous for preventive use on umbilical cord stump

**2010**
- Randomized community-based controlled trials to assess impact of CHX on omphalitis and neonatal mortality: TANZANIA, ZAMBIA

**2011**
- Stakeholder dissemination meeting: NEPAL

Activities:
- Research and Evidence
- Global Policy and Advocacy
- Product and Supply
- Country Implementation and Scale

Chlorhexidine gluconate topical solution monograph officially included in USP34-NF29

CHX added to nEML: NEPAL

Introduce/scale: NEPAL

- Stakeholder dissemination meeting: NEPAL
- Operations research: BANGLADESH
- Product attribute study: BANGLADESH
- Community acceptability study: NEPAL
- Application to WHO EML submitted
- Manufacturer established: NEPAL
- Addendum to application to WHO EML List submitted
- Stakeholder dissemination meeting: BANGLADESH
- Willingness to pay study: BANGLADESH
- CHX pilot introduction: NEPAL (4 districts)
- Product registration: NEPAL
- CHX added to nEML: NEPAL
- Introduce/scale: NEPAL

From Research to Use: Saving Newborn Lives With Chlorhexidine
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>Facility-based, individually randomized controlled trial to evaluate use of CHX on omphalitis: <strong>UGANDA</strong>&lt;sup&gt;17&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Chlorhexidine Working Group (CWG) formally established</td>
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<tr>
<td></td>
<td>Study tour: <strong>MADAGASCAR</strong> to <strong>NEPAL</strong></td>
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<tr>
<td></td>
<td>Formative research: <strong>MADAGASCAR</strong>&lt;sup&gt;18&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>CHX introduction: <strong>NIGERIA</strong> (Sokoto and Bauchi states only)&lt;sup&gt;19&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>CWG technical meeting: <strong>NIGERIA</strong></td>
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<td></td>
<td>Formative research: <strong>NIGERIA</strong></td>
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<tr>
<td>2013</td>
<td>CHX included in Lives Saved Tool (LIST)</td>
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<td></td>
<td>CHX added to Maternal and Neonatal Directed Assessment of Technology (MANDATE) tool</td>
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<td></td>
<td>Liquid and gel forms of CHX added to WHO EML&lt;sup&gt;20&lt;/sup&gt;</td>
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<td></td>
<td>Regional meeting in Francophone West Africa&lt;sup&gt;22&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Manufacturers established: <strong>NIGERIA</strong></td>
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<tr>
<td></td>
<td>Product registration: <strong>BANGLADESH</strong></td>
</tr>
<tr>
<td></td>
<td>Formative research: <strong>ETHIOPIA</strong>&lt;sup&gt;23&lt;/sup&gt; <strong>HAITI</strong>&lt;sup&gt;24&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>CWG technical meeting: <strong>LIBERIA</strong></td>
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<tr>
<td></td>
<td>User preference study: <strong>LIBERIA</strong></td>
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<td></td>
<td>Introduce/scale: <strong>LIBERIA</strong> <strong>MADAGASCAR</strong>&lt;sup&gt;25&lt;/sup&gt;</td>
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<tr>
<td>2014</td>
<td>Liquid CHX product formulation added to UNICEF Supply Division catalog</td>
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<td></td>
<td>CHX for cord care added to WHO postnatal care recommendations&lt;sup&gt;26&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Product registration: <strong>NIGERIA</strong></td>
</tr>
<tr>
<td></td>
<td>Market research: <strong>NIGERIA</strong> to <strong>NEPAL</strong></td>
</tr>
<tr>
<td></td>
<td>CHX added to nEML: <strong>ETHIOPIA</strong> <strong>KENYA</strong> <strong>MADAGASCAR</strong> <strong>MADAGASCAR</strong> <strong>MYANMAR</strong></td>
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<td>Introduce/scale: <strong>AFGHANISTAN</strong> <strong>BANGLADESH</strong> <strong>DRC</strong> <strong>MALAWI</strong> <strong>PAKISTAN</strong>&lt;sup&gt;28&lt;/sup&gt;</td>
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<td>2015</td>
<td>Global Maternal Newborn Health meeting:&lt;sup&gt;29&lt;/sup&gt; <strong>MEXICO CITY</strong></td>
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<td>Manufacturer established: <strong>KENYA</strong></td>
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<td></td>
<td>Product registration: <strong>ETHIOPIA</strong> <strong>KENYA</strong> <strong>MADAGASCAR</strong> <strong>NIGER</strong></td>
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<td>CHX added to nEML: <strong>ETHIOPIA</strong> <strong>KENYA</strong> <strong>MADAGASCAR</strong> <strong>MYANMAR</strong></td>
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<td>CHX added to nEML: <strong>MALI</strong>&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>Market research: <strong>KENYA</strong>&lt;sup&gt;21&lt;/sup&gt;</td>
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<tr>
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<td>CHX added to nEML: <strong>MALI</strong></td>
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<td></td>
<td>Introduce/scale: <strong>BANGLADESH</strong> <strong>ETHIOPIA</strong>&lt;sup&gt;22&lt;/sup&gt; <strong>KENYA</strong>&lt;sup&gt;23&lt;/sup&gt;</td>
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<td></td>
<td>Study tour: <strong>UGANDA</strong> to <strong>NIGERIA</strong></td>
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<td>2016</td>
<td>Sustainability meeting: <strong>ETHIOPIA</strong>&lt;sup&gt;24&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Gel CHX product formulation added to UNICEF Supply Division catalog</td>
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<tr>
<td></td>
<td>Product registration: <strong>ETHIOPIA</strong> <strong>KENYA</strong> <strong>MADAGASCAR</strong> <strong>NIGER</strong></td>
</tr>
<tr>
<td></td>
<td>CHX integrated into the new Demographic Health Survey (DHS) newborn care module</td>
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<tr>
<td></td>
<td>CHX integrated into UNICEF Multiple Indicator Cluster Survey (MICS): <strong>NIGERIA</strong></td>
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<tr>
<td></td>
<td>Formative research: <strong>MALI</strong>&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Market research: <strong>KENYA</strong>&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>CHX added to nEML: <strong>KENYA</strong> <strong>NIGERIA</strong> <strong>PAKISTAN</strong></td>
</tr>
<tr>
<td></td>
<td>Introduce/scale: <strong>MOZAMBIQUE</strong></td>
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<tr>
<td>2017</td>
<td>CHX topical gel monograph was included in the new global health section of USP40-NF35&lt;sup&gt;26&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Product registration: <strong>CAMEROON</strong> <strong>CÔTE D’IVOIRE</strong> <strong>DRC</strong> <strong>LIBERIA</strong> <strong>MOZAMBIQUE</strong> <strong>TANZANIA/ ZANZIBAR</strong> <strong>UGANDA</strong> <strong>ZAMBIA</strong></td>
</tr>
<tr>
<td></td>
<td>CHX added to nEML: <strong>AFGHANISTAN</strong> <strong>GHANA</strong></td>
</tr>
<tr>
<td></td>
<td>National scale-up strategy completed: <strong>NIGERIA</strong>&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>CHX added to nEML: <strong>BNIN</strong> <strong>GHANA</strong></td>
</tr>
<tr>
<td></td>
<td>Introduce/scale: <strong>MOZAMBIQUE</strong></td>
</tr>
</tbody>
</table>

<sup>17</sup> Facility-based, individually randomized controlled trial to evaluate use of CHX on omphalitis: **UGANDA**
<sup>18</sup> Chlorhexidine Working Group (CWG) formally established
<sup>19</sup> CHX introduction: **NIGERIA** (Sokoto and Bauchi states only)
<sup>20</sup> Liquid and gel forms of CHX added to WHO EML
<sup>21</sup> Regional meeting in Francophone West Africa
<sup>22</sup> Manufacturers established: **NIGERIA**
<sup>23</sup> Product registration: **BANGLADESH**
<sup>24</sup> Formative research: **ETHIOPIA** **HAITI**
<sup>25</sup> CWG technical meeting: **LIBERIA**
<sup>26</sup> User preference study: **LIBERIA**
<sup>27</sup> Introduce/scale: **LIBERIA** **MADAGASCAR**
<sup>28</sup> Introduce/scale: **LIBERIA** **MADAGASCAR**
<sup>29</sup> Global Maternal Newborn Health meeting: **MEXICO CITY**
<sup>30</sup> Formative research: **MADAGASCAR**
<sup>31</sup> CWG technical meeting: **LIBERIA**
<sup>32</sup> CHX added to nEML: **ETHIOPIA** **KENYA** **MADAGASCAR** **MYANMAR**
<sup>33</sup> CHX added to nEML: **MADAGASCAR**
<sup>34</sup> Sustainability meeting: **ETHIOPIA**
<sup>35</sup> Product registration: **ETHIOPIA** **KENYA** **MADAGASCAR** **NIGER**
<sup>36</sup> CHX added to nEML: **KENYA** **NIGERIA** **PAKISTAN**
The early days of chlorhexidine: Building the evidence base

Chlorhexidine digluconate is a broad-spectrum antiseptic. Since its development in 1950, chlorhexidine digluconate has been widely used in a range of applications including hand washes, preoperative body shower, wound care, cosmetics, oral hygiene, general disinfection, and veterinary care. In 1998, the World Health Organization (WHO) recognized chlorhexidine digluconate as a suitable antiseptic for cord care.

Between 2002 and 2005, researchers evaluated a new formulation of chlorhexidine digluconate—7.1% chlorhexidine digluconate (CHX)—for umbilical cord care for the first time in a large randomized controlled trial in a developing country, Nepal. The results were remarkable. (See next page.)

In 2005, the United States Agency for International Development (USAID) convened a group of neonatal health experts and researchers in Washington, DC, to review the results of the trial in Nepal and other evidence for the efficacy and safety of CHX to prevent newborn infection in developing countries. The group decided to accelerate introduction of CHX and outlined a multi-pronged approach to move forward with simultaneous research, program, and product planning.

By 2009, researchers conducted two additional randomized controlled trials, which demonstrated the safety and efficacy of CHX for umbilical cord care in Bangladesh and Pakistan. The subsequent meta-analysis confirmed that there was a 23% reduction in neonatal mortality if CHX use began on the first day of life. This dramatic evidence supported the use of CHX and put the intervention on the path to widespread adoption.

FEATURED ACTIVITIES

2002–2005

- Cluster-randomized community-based trial to evaluate impact of umbilical cord cleansing with CHX on neonatal mortality and omphalitis: NEPAL

2005

- USAID and NICHD meeting to review evidence of CHX on infection prevention

2009

- Cluster-randomized community-based trial to evaluate impact of umbilical cord cleansing with CHX on neonatal mortality and omphalitis: BANGLADESH

- Cluster-randomized community-based controlled trial of topical application of chlorhexidine to neonatal umbilical cords for prevention of omphalitis and neonatal mortality in a rural district of Pakistan
Early Evidence: Trials in Nepal, Bangladesh, and Pakistan

In the randomized controlled clinical trials in Nepal, Bangladesh, and Pakistan, CHX liquid was applied on the day of birth, followed by once-daily applications ranging from 7 to 14 days post-birth. The studies were cluster-randomized control trials, resulting in high-grade evidence. More than 90% of the births included in the studies happened at home.

<table>
<thead>
<tr>
<th>STUDY CHARACTERISTIC</th>
<th>Nepal²</th>
<th>Bangladesh⁴</th>
<th>Pakistan⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall neonatal mortality rate (at time of study)</td>
<td>39/1,000</td>
<td>36/1,000</td>
<td>30/1,000</td>
</tr>
<tr>
<td>% of births at home (at time of study)</td>
<td>92%</td>
<td>88%</td>
<td>80%</td>
</tr>
<tr>
<td>Total sample size</td>
<td>15,123</td>
<td>29,790</td>
<td>9,741</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Neonatal mortality Omphalitis*</td>
<td>Neonatal mortality Omphalitis</td>
<td>Neonatal mortality Omphalitis</td>
</tr>
<tr>
<td>Comparison group</td>
<td>Dry cord care</td>
<td>Dry cord care</td>
<td>Dry cord care</td>
</tr>
<tr>
<td>Frequency of application</td>
<td>Days 1, 2, 3, 4, 6, 8,10</td>
<td>a. First 24 hours b. Daily for 7 days</td>
<td>Daily for 14 days</td>
</tr>
<tr>
<td>Intervention provider</td>
<td>Project staff</td>
<td>Project staff</td>
<td>Traditional birth attendant and caretaker</td>
</tr>
</tbody>
</table>

*Omphalitis is an infection of the umbilical stump.

KEY FINDINGS

**Nepal**
- Compared to dry cord care, chlorhexidine cord care reduced newborn deaths among those enrolled in the study by 24% and reduced severe omphalitis by 75%.
- Neonatal deaths were reduced by 34% if chlorhexidine was first applied within 24 hours of birth (but deaths were not reduced among those who had the first application more than 24 hours after birth).

**Bangladesh**
- Single chlorhexidine application on the first day of life reduced newborn deaths among those enrolled in the study by 20%, and moderately reduced severe omphalitis, as well as cord bacterial colonization. Seven-day chlorhexidine application reduced severe cord infection by 65% and reduced bacterial colonization, but neonatal mortality was only 6% lower in this group than among controls (not statistically significant). The investigators concluded that the relative lack of mortality effect in the seven-day chlorhexidine application group had occurred as a result of chance.
- Mortality reduction was greatest in preterm babies.

**Pakistan**
- Neonatal deaths were 38% lower in the chlorhexidine group compared to the dry cord care group.
- Severe cord infection was 42% lower in the chlorhexidine cord care group compared to the dry cord care group.
Improving the product to increase acceptability

Although clinical trials had demonstrated that CHX was safe and effective for umbilical cord care, CHX would need to be affordable and acceptable by health workers, mothers, and other caregivers in order to achieve impact at scale. In 2007, various organizations, including PATH, responded to user needs to make chlorhexidine more acceptable and affordable.

Expanding dosage forms

In Nepal and other countries in South Asia, applying various compounds to the newborn cord stump by finger is a widespread practice, and many felt that a CHX formulation and application method more closely approximating this traditional practice might result in greater user satisfaction and compliance. Results of a small qualitative study in Nepal had suggested that gel or lotion formulations might be more popular than liquid. However, the three randomized clinical trials to date had used liquid formulation, and no research had been conducted to find out whether a gel would be equally effective.

To help answer this question, a study was conducted in Nepal in 2009 to compare bacterial colonization on the umbilical cord cleansed by either chlorhexidine gel or chlorhexidine liquid. Samples collected from nearly 700 newborns from normal deliveries at a hospital in Kathmandu were evaluated. The study also examined the acceptability of gel versus liquid formulations by interviewing users. The study found that the gel was equally effective as liquid in preventing bacteria colonization on the cord that could cause infection. It also found that, while satisfaction and compliance were high for both, more users preferred gel. These results paved the way for inclusion of gel formulation. CHX can now be formulated to be either gel or liquid, which provides options based on local context and user preference.

Ensuring proper use

As with all other medicines, care must be taken to ensure that the product is used appropriately. A 7.1% chlorhexidine digluconate formula can cause serious harm if applied to the eyes and should also not be put into the ear canal. Regardless of the type of primary container and dosage form used, it is critically important that persons and organizations responsible for chlorhexidine for umbilical cord care programs, and also those responsible for the distribution of the product to caregivers, take necessary measures to ensure correct use. Key measures include:

1) Selecting a primary container uniquely associated with CHX, 2) Including appropriate information in the product label, 3) Providing culturally appropriate and easy-to-understand instructions for use (IFU), 4) Providing proper training to health care professionals who interact with mothers and/or provide the product, 5) Developing behavior change programs to achieve accurate user understanding of product use, and 6) Ensuring adverse event reporting for timely intervention and program improvement.
Easy-to-use containers and understandable IFU can also influence product uptake. Between 2008 and 2009, PATH collaborated with Johns Hopkins University and the Projahnmo Maternal Morbidity Study Group operations research in Bangladesh to implement a product attribute study and develop model pictorial IFU to inform these areas. At the time, only liquid chlorhexidine was available, so both studies used that formulation.

The product attribute study assessed preferences of users and service providers for primary containers, applicators, and combinations thereof. The study found that users preferred a dropper bottle, which is a plastic container with a nozzle, because it was easiest to handle. Later, a pharmaceutical company in Bangladesh added a distinctive purple cap to the dropper bottle to ensure proper use, based on feedback from program implementers. CHX in the modified dropper bottle is now being scaled in Bangladesh.

During the same time, PATH developed a model pictorial IFU for liquid CHX (see below). The IFU contained drawings and minimal text so that users with low literacy could easily follow the instructions. These instructions were provided alongside CHX.

**Determining product pricing**

Understanding what users are willing to pay for CHX is critical to building sustainable supply and demand. To help answer that question and inform thinking about other markets, PATH conducted a willingness-to-pay study in Bangladesh in 2010. The study included a household survey of nearly 2,000 couples from rural areas of the country and assessed these couples’ willingness to pay for three types of umbilical cord care products at different price points: a single-dose liquid, a multi-dose liquid, and a single-dose gel formulation.

Results demonstrated that 41% of respondents were willing to pay the prefixed price of Bangladesh Taka BDT27–35 or more for the single-dose liquid, 33% were willing to pay for the prefixed price of BDT45–60 or more for the multi-dose liquid, and 31% were willing to pay for the prefixed price of BDT45–60 or more for the gel formulation.

While the majority of the respondents were not willing to pay the prefixed prices, all participants were willing to pay some amount of money. In addition, for the sake of preventing newborn cord infections, the majority of respondents were willing to cope with higher prices by borrowing money. This willingness to pay for a product that would prevent infection in their newborn was similar across all respondent groups.

Given the pattern of willingness-to-pay and the proposed coping mechanisms to address higher prices, this study recommended that the unit price of a CHX product should range between BDT15 and BDT25 (US$0.21–0.35 at the time of the study) for it to be accessible.

![Instructions for use developed for use with the modified dropper bottle in Bangladesh.](image)
Creating an enabling environment for chlorhexidine

For those involved in accelerating use of CHX in low-resource countries, creating an enabling environment to facilitate uptake became a critical next step. First, the global regulatory and policy environment had to be adapted to be supportive of use of CHX for newborn care, and countries had to develop local policies that aligned with global guidance. Second, a knowledge management mechanism was needed to share information between the global and country levels and to allow countries to leverage their experience and knowledge to accelerate CHX introduction.

The WHO adds CHX to Essential Medicines List

PATH and other groups began to look closely at the WHO’s recommendations on CHX to ensure that ministries of health would have clear global guidance as they made decisions about future adoption of chlorhexidine in their countries. At the time, the WHO Essential Medicines List for Children (EMLc) included CHX under “Disinfectants and Antiseptics,” specifying a solution of 5% (digluconate). However, stakeholders felt that this listing should be changed to better reflect both the use of CHX for cord care and the appropriate concentration of 7.1% CHX for that purpose in order to eliminate confusion among policy makers, regulators, and users.

In 2008, based on the evidence from clinical trials and field research, PATH and USAID jointly submitted an application to the WHO Expert Committee on Selection and Use of Essential Medicines to include CHX for umbilical cord care in the WHO EMLc. Although the evidence from the three randomized controlled clinical trials from the three South Asian countries was sufficient, this application resulted in listing
20% chlorhexidine digluconate with an instruction to dilute for umbilical cord care use due to the absence of a commercially available CHX (7.1% chlorhexidine gluconate) product at that time. PATH, USAID, and other partners continued to work on increasing commercial availability of CHX, and in July 2013, both liquid and gel formulations of CHX (delivering 4% chlorhexidine) for umbilical cord care were included on the WHO EMLc.20

The WHO updates cord care guideline

In 1999, the WHO document entitled “Care of the Umbilical Cord: A Review of the Evidence” recommended that topical antimicrobials be used on the stump in home deliveries “… as a temporary measure, according to a local situation (e.g., in neonatal tetanus endemic areas or to replace a harmful traditional substance).” In addition, WHO recommended that in institutional deliveries, antimicrobials could be used “according to local situation” and specifically identified CHX as one of five recommended antimicrobial agents. In light of new data from the three randomized controlled trials in South Asia, WHO undertook a review of current cord care guidelines.

In 2013, a new recommendation for cord care was approved by the WHO Guidelines Review Committee and included as part of their recommendation on postnatal care of mother and newborn.26 The new recommendation states that “Daily chlorhexidine (CHX aqueous solution or gel, delivering 4% chlorhexidine) application to the umbilical cord stump during the first week of life is recommended for newborns who are born at home in settings with high neonatal mortality (30 or more neonatal deaths per 1000 live births). Clean, dry cord care is recommended for newborns born in health facilities and at home in low neonatal mortality settings. Use of chlorhexidine in these situations may be considered only to replace application of a harmful traditional substance, such as cow dung, to the cord stump.”

To further create an enabling environment for the implementation of chlorhexidine for umbilical cord care, two additional randomized controlled trials were conducted in Africa beginning in 2010. Although substantial reductions in mortality were seen in trials in South Asia, application of 7.1% chlorhexidine to the umbilical cord did not significantly reduce neonatal mortality rate in the study sites in Tanzania or Zambia. This means that study results from the five randomized controlled trials have shown an impact on mortality risk in populations with high NMR (30–40 deaths/1,000 live births) and have not shown measurable impact on mortality risk in populations with low NMR (≤ 17 deaths/1,000 live births). Further, in high-mortality settings, use of 7.1% chlorhexidine on the umbilical cord reduced deaths regardless of whether infants were born at home or in a facility.38,39

Finally, the application of 7.1% chlorhexidine to the umbilical cord reduces risk of omphalitis, even in low-mortality settings where there is no evidence of impact on overall newborn mortality risk. An additional trial in Uganda is currently underway to assess omphalitis risk when a single application of CHX is used on infants born in facilities.17

### REDUCTION IN NEONATAL MORTALITY RATE (NMR) IN 5 RANDOMIZED CONTROLLED TRIALS.

<table>
<thead>
<tr>
<th>Country</th>
<th>NMR (/1,000) in dry cord care/control arm</th>
<th>NMR (/1,000) in chlorhexidine arm</th>
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</thead>
<tbody>
<tr>
<td>Pakistan*</td>
<td>33.8</td>
<td>24.9</td>
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<tr>
<td>(n = 9,741)</td>
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</tr>
<tr>
<td>Bangladesh*</td>
<td>28.3</td>
<td>22.5</td>
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<tr>
<td>(n = 29,790)</td>
<td></td>
<td></td>
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<tr>
<td>Nepal*</td>
<td>19.3</td>
<td>14.6</td>
</tr>
<tr>
<td>(n = 15,123)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zambia</td>
<td>13.6</td>
<td>15.2</td>
</tr>
<tr>
<td>(n = 37,865)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanzania</td>
<td>11.7</td>
<td>10.5</td>
</tr>
<tr>
<td>(n = 36,911)</td>
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</tbody>
</table>

* Statistically significant at 95% confidence interval.
Global collaboration for country introduction and scale: The Chlorhexidine Working Group

In 2012, PATH, in collaboration with the Bill & Melinda Gates Foundation and USAID, developed the background paper on CHX for the UN Commission for Life-Saving Commodities for Women and Children (UNCoLSC). This background paper helped to provide guidance for global health leaders on how and why CHX should be prioritized as part of a package of 13 priority interventions identified by the UNCoLSC as critical to maternal and child health. As a result, the Chlorhexidine Working Group (CWG), an international collaboration of organizations with diverse membership, was formally organized. The aim of the CWG is to further advance use of CHX through technical assistance and advocacy, and PATH was selected to serve as the secretariat.

The CWG aims to achieve the maximum sustainable benefit for public health. Collaboration is a key element of the CWG approach, which draws upon the expertise of its members and partners in areas such as product development, manufacturing, supply chain, policy, regulatory, program design and implementation, quality assurance, and training. The CWG focuses on the following three areas:

1. Supporting in-country decision-making for policy and strategy development

The CWG supports country-driven development of policy and clinical guidelines, as well as sustainable introduction and scale of the CHX implementation in newborn care programs. CWG support includes guidance on appropriate product form, administration regimen, and development of introduction and scale-up strategies for CHX. In support of development of sustainable programs, the CWG also provides assistance with formative research to select the user-preferred dosage form and market research to inform product distribution and communication strategies to reach the target audience.

2. Establishing quality-assured regional supply bases

The CWG has worked with manufacturers, ministries of health, and regulatory authorities in sub-Saharan Africa and South Asia to select appropriate supply-side strategies, to establish regional production bases as appropriate, and to ensure the sustainable availability of quality-assured CHX for umbilical cord care. The breadth of the CWG’s commitment in this area extends from manufacturer assessment and selection to provision of technical assistance to manufacturers to enable them to produce the product in compliance with the WHO Good Manufacturing Practices (GMPs) and register their products with their national regulatory authorities.

3. Managing knowledge and resources

The tools and guidance documents that have been developed to date include a technical brief that summarizes evidence and availability of CHX including recent data, a list of frequently asked questions, guidance documents for national policy and program development, interview guides for formative research, pictorial instructions, behavior change communication materials for providers and families, a market sizing tool, and a tool to estimate the cost of scale-up. These tools and guidance documents are publicly shared by being posted on the Healthy Newborn Network website (http://www.healthynewbornnetwork.org/issues/) and are updated on a regular basis.

CHX resources are posted and shared through the Healthy Newborn Network website.
Membership includes:

- PATH [CWG Secretariat]
- Ayzh
- Bill & Melinda Gates Foundation
- Boston University
- Burnet Institute
- Centre for Infectious Disease Research in Zambia
- Clinton Health Access Initiative
- Drugfield Pharmaceuticals Ltd. (Nigeria)
- Duke University
- GSK (UK)
- Global Health Action
- Jhpiego
- John Snow, Inc.
- Johns Hopkins Bloomberg School of Public Health
- Johnson & Johnson (USA)
- Lomus Pharmaceuticals Pvt. Ltd. (Nepal)
- Ministry of Health, DRC (Reproductive Health)
- Ministry of Health, Ethiopia (Maternal and Child Health)
- Ministry of Health, Kenya (Child and Adolescent Health)
- Ministry of Health, Liberia (Family Health)
- Ministry of Health, Malawi (Reproductive Health)
- Ministry of Health, Mozambique (Child Health)
- PSI
- Promoting the Quality of Medicines/United States Pharmacopeia
- Save the Children/Saving Newborn Lives
- SHOPS Plus/Abt Associates
- Systems for Improved Access to Pharmaceuticals and Services/Management Sciences for Health
- United Nations Children’s Fund
- United States Agency for International Development
- Universal Corporation Ltd. (Kenya)
- University of Illinois at Chicago School of Nursing
- University Research Co., LLC/Center for Human Services
- World Health Organization
Shaping local and regional markets to increase use of chlorhexidine

Simultaneously, the CWG and partners turned their attention to creating and shaping the country and regional markets that would allow CHX to be widely adopted. However, several challenges still existed. For example, even in countries with high neonatal mortality, knowledge was low among country decision-makers and medical professionals about CHX as a product. Distribution strategies for each country needed to be developed based on clear understanding of the market, but in many places the levels of demand by mothers and other caregivers for CHX was unknown. To that end, the CWG adopted a multi-pronged approach.

Building awareness and demand at the country level

Awareness raising and policy alignment are the first steps in market shaping. Since country policy makers were not well aware of the new WHO recommendation and the inclusion of CHX on the WHO EML, the efforts of the CWG at the country level began with raising awareness about the global evidence. Understanding global guidance would enhance the ability of country decision-makers to include CHX in national policy and clinical guidelines.29,41

The CWG also provided technical support so countries could make appropriate decisions on product form (gel or liquid), application regimen (one-day, seven-day, or some other length of application), and use in facility, community, or both. The CWG provided evidence, examples from other countries, and global policy and recommendations. The group also supported country ownership and leadership in the decision-making process.

Building awareness and demand at the regional level

The CWG realized that knowledge sharing between countries was equally important to raising awareness at the country level. This type of exchange could enhance learning and accelerate CHX uptake regionally.

In September 2011, PATH, USAID, John Snow (JSI), and partners organized the first regional meeting on CHX in Nepalgunj, Nepal.14 Experts, researchers, product specialists, and key program planners from Bangladesh, Cambodia, India, Indonesia, Nepal, and Pakistan participated in this meeting in order to examine the scientific evidence from clinical trials conducted on CHX in the three South Asian...
countries and to discuss how to move forward with CHX work. At the end of the meeting, delegations from the six countries committed to hold national stakeholder consensus meetings on the introduction of CHX as part of newborn care. Specifically, Bangladesh, Nepal, and Pakistan have introduced CHX and are scaling it up nationally.

The CWG’s assistance to four countries in Francophone West Africa—Burkina Faso, Côte d’Ivoire, Niger, and Senegal—is another example. In 2013, a meeting in Burkina Faso, coordinated by JSI, brought together ministry of health (MOH) and nongovernmental organization (NGO) representatives to hear more about the clinical and operational evidence for CHX and share their situations, experiences, and challenges. Countries that had already committed to CHX, including the DRC, Madagascar, and Nigeria, attended to share their experience. As a result of this meeting, all four countries committed to next planning steps to consider introduction of CHX into their newborn programs.22

Niger especially showed strong commitment to introduce the CHX intervention. The CWG provided subsequent technical assistance to Niger in 2015 and helped the country develop the preliminary national scale-up strategy and articulate the budget required for procurement of the commodity.

Providing resources and technical support for market development

The CWG has played an active role in working with countries to understand markets and generate demand for CHX. In 2014 and 2015, PATH performed market research in Nigeria27 and Kenya31 to identify effective communication and distribution strategies for the product and to investigate whether private-sector channels could be utilized for CHX and, if so, what messages should be emphasized. This research explored whether women had used cord care substances for their previous child, what substances they had used, when and where they had obtained them, whether they had purchased the substances, and how much they had paid.

The market research highlighted the similarities and differences between Nigeria and Kenya in the use of cord care substances, the timing of use, where
they were obtained or purchased, and the prices that women pay for them. This information has provided valuable insights for informing decision-making around market strategies. For example, in Nigeria using retailers to distribute CHX would be a reasonable strategy. In Kenya, however, use of retailers could be used to augment other distributors. Differentiating CHX from existing cord care substances, especially methylated spirits, will be important for both countries; however, in Kenya the context-specific strategy will require articulating the benefits of CHX compared to dry cord care in those areas where suboptimal hygienic conditions prevail. Finally, in both countries, the price paid for existing cord care substances will likely become the reference price upon which the price paid for CHX should be based. These market research results have already been used to inform national scale-up strategy in Nigeria and Kenya.

Developing demand generation tools

To support demand generation efforts for CHX, the USAID Center for Accelerating Innovation and Impact, working with many partners, designed a toolkit for countries and communities that are in the process of introducing and scaling chlorhexidine. This work uses Nigeria as a representative example and includes lessons learned from the successful efforts of other countries. Drawing upon insights from research conducted in Nigeria, this guide helps users better understand, capture, and document representative “birth stories,” and how to generate concepts designed to create demand.

Ensuring sustainability

As an increasing number of countries are introducing and scaling up CHX, providing opportunities for early adopter countries to share their experiences and discuss challenges and opportunities is critical to improving program sustainability. To facilitate this, in June 2016 the CWG convened a meeting in Addis Ababa, Ethiopia, that included 34 ministry of health officials, donors, and implementing partners from the Democratic Republic of the Congo (DRC), Ethiopia, Kenya, Liberia, Madagascar, Malawi, Mozambique, Nepal, and Nigeria as well as United States Agency for International Development (USAID), WHO, United Nations Children’s Fund (UNICEF), Saving Newborn Lives, Maternal and Child Survival Program, Last Ten Kilometers Project, and Save the Children.

The first day consisted of a site visit to Dugda Woreda in East Shoa, where participants interacted with staff from the district health office, Meki Health Center, and Hate Leman Health Post that are delivering CHX as part of the community-based newborn care package. The group visited families with newborns who received the CHX product. The second day consisted of a workshop in which participants:

- Shared recent evidence and country-level experience of introducing and scaling the chlorhexidine for umbilical cord care intervention.
- Disseminated tools and resources to assist in long-range planning.
- Identified goals for the next 3–5 year period and planned next steps for sustainable programming of the intervention in their countries.

A design toolkit for the development of demand generation materials.
Increasing supply of chlorhexidine

As more countries explored introducing CHX, product availability became a critical issue. Choosing an appropriate product sourcing strategy to ensure a sustainable supply of good-quality CHX was a pivotal decision that would influence widespread adoption and long-term success. The CWG initially considered two strategies for manufacture of this commodity. The first was production and global distribution by a multinational company. The second was production and regional distribution by locally owned companies or subsidiaries of multinational companies that were based in low- and middle-income countries (LMIC).

The CWG opted for a local production strategy with regional distribution, which meant establishing production bases in selected LMIC. These bases could then become regional hubs able to leverage local manufacturers’ regional distribution networks. This strategy made sense for several reasons. First, because CHX is a topical antiseptic, its risk profile is low when used as directed. Second, manufacturing CHX does not require unique ingredients or special manufacturing equipment. Lastly, in recent years pharmaceutical companies in some LMIC have gained the ability to produce good-quality pharmaceuticals.

Because gaining WHO prequalification or approvals from stringent regulatory bodies is costly and could prevent manufacturers from taking on a product like CHX, which has a low profit margin, manufacturers are not currently required to obtain them. Instead, PATH, United States Pharmacopeia (USP), and the CWG have undertaken a number of activities focused on ensuring good-quality production by manufacturers in LMIC. These activities include technical assistance for manufacturers and monographs to guide product development.

Assessments of and technical assistance for local manufacturers

PATH collaborated with the Promoting the Quality of Medicines program at United States Pharmacopeial Convention (PQM/USP) to assess and identify manufactures that could make a good-quality product and that were also committed to the product’s public health benefits. PATH and PQM/USP sought interest from in-country manufacturers, performed rapid assessments to short list manufacturers that were eligible for technical assistance, and engaged them in joint product development activities. The assessments and technical assistance have resulted in the establishment of local production facilities in several LMIC, allowing for the supply of high-quality CHX.

### FEATURED ACTIVITIES

- **2008**
  - Manufacturer established: NEPAL

- **2009**
  - Product registration: NEPAL

- **2011**
  - Chlorhexidine gluconate topical solution monograph officially included in USP34-NF29

- **2013**
  - Manufacturers established: NIGERIA, BANGLADESH
  - Product registration: BANGLADESH

- **2014**
  - Liquid CHX product formulation added to UNICEF Supply Division catalog
  - Product registration: NIGERIA

- **2015**
  - Manufacturer established: KENYA
  - Product registration: ETHIOPIA, KENYA, MADAGASCAR, NIGER

- **2016**
  - Gel CHX formulation added to UNICEF Supply Division catalog
  - Product registration: BENIN, GHANA

- **2017**
  - CHX topical gel monograph was included in the new global health section of USP40-NF35
  - Product registration: CAMEROON, CÔTE D’IVOIRE, DRC, LIBERIA, MOZAMBIQUE, TANZANIA/ZANZIBAR, UGANDA, ZAMBIA

Activities: Product and Supply, Global Policy and Advocacy
assistance, conducted GMP assessments of those companies to identify areas for improvement, and helped manufacturers develop corrective action plans. Ongoing monitoring and technical assistance to manufacturers were also provided until they registered their products with their national regulatory authorities.

Developing USP monographs for CHX gel and liquid

Monographs describe the properties, claims, indications, and conditions for pharmaceuticals. The USP created monographs for CHX gel and liquid. The monograph for CHX topical solution was included in USP-NF, and the monograph for CHX gel was included in the new global health section of USP-NF. Manufacturers and procurers of CHX can now use the monographs to test the quality of the product.

Creating standardized information for manufacturers and procurers

To support the quality of CHX manufacturing and procurement, the CWG created a number of materials that are available on the Healthy Newborn Network website. These include a standardized patient information leaflet, which guides manufacturers in developing easily understandable, accurate, and consistent product information for users. The CWG also created a list of key factors that procurers should consider when purchasing CHX.

Increased access to CHX products

With CWG support, CHX is now produced by local manufacturers in four countries (Bangladesh, Kenya, Nepal, and Nigeria) and is available in domestic and export markets. One multinational company is poised to act as a back-up supplier as needed. Through 2016, approximately 5.5 million units of CHX have been distributed by these manufacturers. UNICEF also distributed approximately 2.7 million units of CHX through 2015. In addition, CHX products are registered in more than 15 countries.

Examples of current formulations and sizes of products offering from manufacturers in LMIC.
Bringing it all together: Taking chlorhexidine to scale in Kenya

The product and market development efforts around CHX have all pointed toward one goal: supporting ministries of health and partners to introduce and scale up CHX intervention as part of essential newborn programming and sustain its proper use to achieve health impact. While Nepal was the first country to adopt CHX into its essential package of care for newborns\textsuperscript{10,16} and Nigeria is also on the way to scale CHX\textsuperscript{19,35} (see page 19), as of 2017 dozens of other countries are either introducing or scaling CHX or are planning to introduce it in the near future. One example of a multifaceted approach in Kenya aligns policies, guideline development, product introduction, training to service providers, demand generation, and monitoring and evaluation, which is critical for seamless program implementation and to achieve sustainability.

PATH has been working with the Kenyan Ministry of Health to introduce and scale up CHX nationally since 2013. The Kenyan Ministry of Health has recognized the importance of CHX to reduce neonatal infections and committed to introduce and scale up CHX in its essential newborn care package. In support of this effort, PATH has provided support to the government in a number of areas as noted below.

**Providing technical assistance to formulate policy and guidelines**

Drawing on its experience assisting other countries, as well as tools and materials developed by the CWG, PATH provided technical assistance to assist the country in formulating policy and clinical guidelines. Working under the leadership of the MOH’s newly established Newborn Technical Working Group, PATH supported the review of newborn policies to include use of CHX in 2014. As a result, CHX gel and liquid were included in Kenya’s national essential medicine list in 2016.\textsuperscript{45}

Clinical guidelines, which clarified that CHX

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**FEATURED ACTIVITIES**

2011

- Introduction and scale: **NEPAL**\textsuperscript{10,34}

2012

- Introduction and scale: **NIGERIA** (Sokoto and Bauchi states only)\textsuperscript{19}

2013

- Introduction and scale: **LIBERIA, MADAGASCAR**\textsuperscript{25}

2014

- Introduction and scale: **AFGHANISTAN, DRC, MALAWI, PAKISTAN**\textsuperscript{28}

2015

- CWG technical meetings: **KENYA, MOZAMBIQUE**
- Market research: **KENYA**\textsuperscript{17}
- Introduction and scale: **BANGLADESH, ETHIOPIA, KENYA**\textsuperscript{32}

2016

- National scale-up strategy completed: **NIGERIA**\textsuperscript{35}
- Introduction and scale: **MOZAMBIQUE**

Activities:  ● Country Implementation and Scale
program design for initial implementation of CHX in Nyanza and Western regions.

Implementing CHX in five counties in Nyanza and Western regions to inform scale-up

Between December 2015 and September 2016, PATH worked with the MOH to implement the first phase of product scale-up. To do this implementation research, PATH leveraged the AIDS, Population and Health Integrated Assistance (APHIAplus) Western Kenya project as a foundation for the introduction of chlorhexidine in five counties in the Western and Nyanza regions. The APHIAplus Western Kenya Project, funded by USAID from 2011–2017, was implemented by a consortium led by PATH to improve key health indicators.

CHX was introduced at health facilities that provide reproductive, maternal, newborn, and child health services. As part of routine antenatal care, pregnant women were educated about CHX and provided with the product. They were also asked to bring the product to health facilities at the time of delivery, where CHX was then applied to the umbilical cord. CHX was also provided at health facilities to mothers who did not bring CHX with them. Mothers were then instructed to continue to apply CHX when they returned home.

Six indicators were developed to track progress of the introduction and access to and coverage of CHX. The initial introduction in the five counties was successful overall. By the end of August 2016, approximately 32,000 newborns, or 91% of the initial target population, had received CHX applications. Health facilities have now become a more common source from which to obtain cord care substances (i.e., CHX), and antenatal care has become the more common avenue through which to obtain cord care information. The practice of applying CHX immediately after cord cutting has been standardized, and the reason for applying CHX to prevent cord care infection has become much better understood by mothers and service providers. The results from this initial implementation were shared with the MOH, county health departments, and other program implementers. PATH has continued to assist the MOH in scaling up use of CHX and incorporating lessons learned from the initial implementation into the MOH newborn annual work plan and activities.

Establishing a local production base

In collaboration with PQM/USP, PATH identified a handful of pharmaceutical manufacturers eligible for technical assistance to support CHX production. One of the manufacturers, Universal Corporation Limited, has now registered its CHX gel product with the Pharmacy and Poisons Board, the national regulatory authority in Kenya. Since then, Universal’s product has been used in Kenya and exported to other countries.

Conducting market research

In 2015, PATH undertook market research to help the Kenyan government better understand the landscape and market for CHX and to develop effective communication and distribution strategies. The research identified government health care facilities as important distribution points for CHX and demonstrated that it would be well received by pregnant women and their family members. The research also provided important market segmentation data and pinpointed effective distribution and communication strategies for reaching those segments. The results of the research contributed to should be used once daily for seven days, were also developed in 2015 and modified in 2016 based on the initial implementation in the Nyanza and Western regions.

Counseling a new mother about CHX use in Kenya.
Nepal

A pioneer in CHX scale-up

In late 2011, Nepal became the first country in the world to introduce chlorhexidine for umbilical cord care and commit to scale its use nationwide. This countrywide introduction is the result of many years of effort on the research-to-use journey. In 2002 in Nepal, the first cluster-randomized community-based trial evaluated the impact of CHX on neonatal mortality when applied to the umbilical cord and then went on to pioneer the introduction and scale of CHX. In 2012, following a pilot of the intervention in four districts, the community-based newborn care program integrated facility and community programming nationwide. By 2017, Nepal had achieved remarkable results: treating 1.8 million newborns and reaching with 100% coverage in the target population, which has meant the lives of 9,300 newborns have been saved.

Nigeria

Leading the way in sub-Saharan Africa

The Federal Ministry of Health (FMOH) and a set of key partners, including PATH, laid the groundwork to scale chlorhexidine across Nigeria. Under FMOH’s leadership, USAID Center for Accelerating Innovation and Impact—in close partnership with USAID/Nigeria, Clinton Health Access Initiative, and Maternal and Child Survival Program—developed a National Strategy and Implementation Plan for CHX in 2016. The plan, which is integrated with the country’s maternal, newborn, and child health plans, identifies a national objective of CHX uptake of 52% over a five-year period. It lays out a comprehensive strategy that guides programming, resource allocation, and commitments to reach that goal.

The comprehensive plan was informed by strategies and lessons learned from a number of development partners including the USAID Targeted States High Impact Project. More than 50 government departments, development partners, and donors were interviewed. The strategy was also guided by market research conducted by PATH in 2015 that identified the current practices around childbirth including cord care, explored perceptions and preferences for CHX, and identified effective distribution and communication strategies to reach high-priority market segments.
Collaboration, the key to success

The journey of CHX from an antiseptic not widely used for cord care to an intervention that has been adopted around the world to save babies’ lives could not have happened without the collaboration and dedication of many individuals and organizations across geographies and around the world. At the same time, strong leadership and coordination of effort made by these individuals and organizations will enable seamless introduction, while an evidence-based and country-driven approach will make programs sustainable for a longer period of time. Over the last decade, a number of lessons that reinforce the theme of collaboration have emerged:

- **Collaboration with ministries of health and other organizations is key to seamless introduction.** Ministry of health interest and readiness must be cultivated alongside non-governmental implementing partners so that introduction occurs at the time that is right for the country.

- **Collaboration with private sector is important for creating uninterrupted supply and access.** Because CHX is a low-profit-margin, low-volume product, understanding how to incentivize manufacturers is an integral part of the CHX supply strategy. Leveraging private-sector channels for product distribution and demand generation could also be helpful in improving access. However, use of private-sector channels including retailers requires careful consideration. Not all countries will have active, sustainable private-sector channels and not all products are suitable for private-sector distribution. In addition, if the in-country regulatory system is too weak to provide effective oversight to the private-sector channels, using private-sector channels may have unintended adverse consequences, such as illegitimate or sub-optimal products entering the market.

- **Strong coordination ensures that multiple collaborations can happen in a timely manner and that information is shared among all partners.** The CWG secretariat acts as a hub for all partners at the global level. This working group coordinates all relevant stakeholders, translates information back and forth between the global and country levels, and inspires and manages country-level expectations and actions. At the country level, an uptake coordinator could coordinate efforts by in-country stakeholders and ensure synergy and seamless implementation of CHX.

- **Donor funding is a key to kick-start program introduction in low-income countries, but transition from donor-funded programs to government-led programs is required to achieve sustainability.** Securing donor funding for product introduction and scale-up might be required at an initial stage. Assess national planning capacity to translate donor-funded pilot efforts into national scale. Donors must select the right partner and fund the right process to work with government to develop a country-led sustainable implementation effort.

- **Supporting country-led, evidence-based policy making helps develop and sustain programs that fit countries’ health systems.** Countries do not necessarily have a process and knowledge to effectively use results of market research or implementation research for policy making or programming. Involving the MOH in generating research questions, informing them of interim results, and disseminating results and discussing their implications with the MOH will enable implementation research results to be effectively translated into policy making and sustainable programming. As the product moves from the introduction to scale-up phase, the ministry of health should take a more significant role and stronger leadership.
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