Chlorhexidine end-to-end analysis focusing on Uttar Pradesh

Prepared for Chlorhexidine Working Group
December 2012
Joel Segre
# Background on Chlorhexidine (CHX)

## Chlorhexidine
- First use in 1956
- Broad spectrum antiseptic
- Common uses in veterinary, dental, and wound care
- Completely commoditized, commonly sold in 50L drums
- Inexpensive & globally available

## Chlorhexidine for cord care
- Commonly used in wealthy countries through the 1980s
- Exemplary safety record
- Superior clinical efficacy in septic environments, even when compared with other antiseptics
- Easy to apply, good evidence of correct use in communities
- Low cost
- 7.1% chlorhexidine gluconate (also called chlorhexidine digluconate) yields 4% free chlorhexidine

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**Sources:** Medichem; Bhutta; Mullany; Lomus; Photos from Bhutta et al, Stanford Medical Center, Auckland District Health Board
There have been three large randomized controlled trials on 7.1% chlorhexidine gluconate for cord care in South Asia

<table>
<thead>
<tr>
<th>Study Characteristic</th>
<th>Nepal</th>
<th>Bangladesh</th>
<th>Pakistan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall NMR</td>
<td>30/1000</td>
<td>36/1000</td>
<td>30/1000</td>
</tr>
<tr>
<td>(at time of study)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Home Births</td>
<td>92%</td>
<td>88%</td>
<td>80%</td>
</tr>
<tr>
<td>(at time of study)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample Size Total</td>
<td>15,123</td>
<td>29,760</td>
<td>9,741</td>
</tr>
<tr>
<td>Primary Outcomes</td>
<td>Mortality</td>
<td>Mortality</td>
<td>Mortality</td>
</tr>
<tr>
<td></td>
<td>Omphalitis</td>
<td>Omphalitis</td>
<td>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>Freq of Multiple App</td>
<td>1,2,3,4,6,8,10</td>
<td>1,2,3,4,5,6,7</td>
<td>Daily for 14 days</td>
</tr>
<tr>
<td>Intervention provider</td>
<td>Project staff</td>
<td>Project staff</td>
<td>TBA &amp; Caretaker</td>
</tr>
</tbody>
</table>

Meta analysis of 3 large trials show 23% reduction in mortality and 68% reduction in cord infection with CHX

Define the intervention | Prove efficacy & effectiveness | Define the product | Manufacture | Gain regulatory approval / endorsement | Initiate local coverage | Sustain local use

**Neonatal mortality: 23% reduction**

<table>
<thead>
<tr>
<th>Mortality in CHX vs. No CHX groups</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepal</td>
<td>0.76 (0.58, 1.00)</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>0.88 (0.74, 1.04)</td>
</tr>
<tr>
<td>Pakistan</td>
<td>0.62 (0.45, 0.85)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.77 (0.63, 0.94)</td>
</tr>
</tbody>
</table>

- Reduction in mortality is correlated with early introduction of chlorhexidine (<24 hrs after birth)
- Additional applications of chlorhexidine after the first day may not have large effects on mortality

**Severe infection: 68% reduction**

<table>
<thead>
<tr>
<th>Severe Infection in CHX vs. No CHX groups</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nepal</td>
<td>0.25 (0.12, 0.50)</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>0.55 (0.30, 1.01)</td>
</tr>
<tr>
<td>Pakistan</td>
<td>0.22 (0.12, 0.42)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.32 (0.18, 0.57)</td>
</tr>
</tbody>
</table>

- Reduction in severe cord infections are correlated with repeat application of chlorhexidine
- Incidence of visible cord infection and mortality do not appear correlated

As with other products, end-to-end analysis reveals that medical needs are only half of the target product profile.
In UP, there is a strong desire to dress the cord stump; 83% of mothers apply some substance to the cut cord.

Most mothers in UP are aware of the risk of infection and wish to minimize it.

“We applied mustard oil to the cord stump to prevent infection… if no mustard oil is put then the cord stump could get infected.”

Across the state, 83% of mothers apply some substance to the cord stump (n=4472)

<table>
<thead>
<tr>
<th>Western</th>
<th>Central</th>
<th>Eastern</th>
</tr>
</thead>
<tbody>
<tr>
<td>90%</td>
<td>73%</td>
<td>88%</td>
</tr>
<tr>
<td>10%</td>
<td>27%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Commonly applied substances include:
- Mustard Oil (46% of respondents)
- Ghee
- Turmeric
- Linseed oil
- Powders & ointments (next page)

Source: Varma et al. Increasing Postnatal Care Of Mothers And Newborns Including Follow-up Cord Care And Thermal Care In Rural Uttar Pradesh. J of Family Welfare. Vol 56 2010
Without a specific product for cord care, some mothers seek medicines associated with infection prevention and treatment.

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**Table: Re-purposing of other medicines for umbilical cord care**

<table>
<thead>
<tr>
<th>Product</th>
<th>Chloromycetin</th>
<th>Neosporin</th>
<th>Gentian Violet</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Price</strong></td>
<td>Rs. 50 (1/caplet)</td>
<td>Rs. 22</td>
<td>Rs. 5</td>
</tr>
<tr>
<td><strong>Community uses</strong></td>
<td>Umbilical care</td>
<td>Wound Care</td>
<td>Umbilical care</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Uttar Pradesh</td>
<td>Uttar Pradesh</td>
<td>Bihar</td>
</tr>
</tbody>
</table>

**In-Community Comparables**

- Demonstrate the price range
- Demonstrate the supply chain
- Demonstrate the demand

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Source: Synovate
When presented with CHX, the majority of Nepalis prefer gel formulations; qualitative work in Nigeria and India is similar.

### Nepali Formulation Preferences

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gel</td>
<td>75%</td>
</tr>
<tr>
<td>Liquid</td>
<td>25%</td>
</tr>
</tbody>
</table>

Gel is viewed as:
- More potent
- Easier to dispense
- More likely to stay in place
- “Warmer”

Formative work in other countries suggests similar preferences:

- The majority of 100+ respondents in UP preferred gel (2011)
- 40+ respondents in Nigeria in Sekoto state preferred gel (2012)
- A survey in Zambia showed a preference for liquid, but did not allow respondents to interact with both products, and therefore may not have provided a valid, direct comparison.

Source: B. Sooli et al, Chlorhexidine Package Preferences among mothers in Southern Province (Zambia); S. Hodgins, Nepal Family Health Program JSI, June 2009
Gel has proven to be as effective as (and possibly more effective than) liquid formulations of chlorhexidine

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**Liquid and gel antiseptic performance**

<table>
<thead>
<tr>
<th></th>
<th>Prior to Application</th>
<th>24hrs Post Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid</td>
<td>29.4%</td>
<td>10.7%</td>
</tr>
<tr>
<td>Gel</td>
<td>33.9%</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

Customer preference should dictate formulation used

- In Uttar Pradesh, gel is the clear preference
- Liquid and gel formulations manufactured by Lomus and Popular Pharma below

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Source: Hodgins et al. Chlorhexidine Gel Versus Aqueous for Preventive Use on Umbilical Stump A Randomized Noninferiority Trial. *The Pediatric Infectious Disease Journal* November 2010
Formulation, instructions for use, and retail packaging must all be designed to fit the target population.

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**Formulation**

- pH: 5.5 - 7.0
- Viscosity: 3,000-5,000 cp
- Potency: 90%-110% assay
- Color: Nearly colorless
- Scent: Not specified
- Shelf Life: Not specified

**Pictorial Instructions for Use**

Field work in Bangladesh and Nepal provided opportunity to iterate on instructions for use, ultimately yielding the above package insert, which uses the yellow color to echo mustard oil, traditionally applied to the cord.

**Retail Packaging**

The name “Kawach” means “Shield”. Packaging in a collapsible tube and box conveys a medicinal product, although sachet packaging would have been less expensive.

Source: PATH; Lomus Pharmaceuticals
There are at least 10 suppliers of CHX concentrate and 61 suppliers of finished CHX products in India alone.

There is no shortage of CHX manufacturing capacity in India:

- Changing the concentration of a chlorhexidine product is a trivial process since they are almost all made from 20% concentrate.
- The market for 5% CHX products appears relatively uninteresting to Indian CHX manufacturers despite its inclusion in the Indian and WHO lists of essential medicines.
- The market for 0.2%, by contrast, has a wide proliferation of brands, likely due to consumer demand for oral rinses and other fast moving products.

### Number of Indian Brands of CHX Products by Concentration

- 0%: 0 brands
- 0.2%: 2 brands
- 0.4%: 4 brands
- 1.1%: 10 brands
- 2.3%: 4 brands
- 2.8%: 2 brands
- 4.0%: 0 brands
- 11.3%: 3 brands

Total: 76 products across 62 Indian manufacturers.
Manufacturing of chlorhexidine is a commoditized process using readily available techniques and equipment

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Manufacturing Process

- Quality check and dispense raw materials
- Preparation of gel (guar gum and water)
- Prepare drug solution (CHX, water, and BAK)
- Mix drug solution and gel
- Add perfume, adjust pH
- Fill & Crimp
- Package & Ship

Manufacturing Equipment

- Mixing equipment used to produce CHX gel at Lomus
- Tube filling equipment used to produce CHX product at Lomus

Source: Lomus Pharmaceuticals
Ingredients of chlorhexidine gel are inexpensive; packaging and overheads drive manufacturing costs

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</thead>
</table>

**Product Cost Components**

<table>
<thead>
<tr>
<th>Formula Component</th>
<th>Formulation</th>
<th>Cost/3g</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>20% CHX gluconate, BP</td>
<td>7.10%</td>
<td>$0.004795</td>
<td>Vipor Chemicals</td>
</tr>
<tr>
<td>50% benzalkonium chloride (optional)</td>
<td>0.10%</td>
<td>$0.000000</td>
<td>Alibaba</td>
</tr>
<tr>
<td>Guar gum, NF</td>
<td>1%</td>
<td>$0.000060</td>
<td>Alibaba</td>
</tr>
<tr>
<td>Sodium Hydroxide, NF</td>
<td>pH to 6.0</td>
<td>$0.000009</td>
<td>Alibaba</td>
</tr>
<tr>
<td>Purified water, USP</td>
<td>Remainder</td>
<td>$0.000001</td>
<td>UP Water Tariffs</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>$0.004865</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Packaging Component</th>
<th>Per Unit</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-printed collapsible aluminum tube</td>
<td>$0.04</td>
<td>Pefect Tubes Pvt</td>
</tr>
<tr>
<td>Printed paperboard box</td>
<td>$0.04</td>
<td>Lomus Pharma Pvt</td>
</tr>
<tr>
<td>Printed color package insert</td>
<td>$0.01</td>
<td>Lomus Pharma Pvt</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>$0.09</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
<th>Per Unit</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staff, Plant &amp; Equipment, QC, Overheads, Profit</td>
<td>$0.05-0.15</td>
<td>Lomus Pharma Pvt</td>
</tr>
</tbody>
</table>

**Target Cost**

$0.15-$0.25 Per Baby

(Lomus manufacturer’s price for Kawach is $0.24 USD)

All costs in USD
The current WHO recommends topical antimicrobials where “necessary, according to local situation”

Stakeholders may benefit from a reminder on the WHO recommendation

- There is a misunderstanding that the WHO strictly recommends dry cord care
- The WHO recommends antimicrobials “according to local situation” and specifically to “replace a harmful traditional substance” like those used in Uttar Pradesh
- The WHO specifically recommends chlorhexidine among other antimicrobials, and notes that 4% solutions are effective

A new recommendation is expected in 2013

Source: WHO. Care of the Umbilical Cord. A Review of the Evidence. WHO RHT MSM 98.4
CHX 5% is on the WHO Essential Medicines List for Children and India’s National List of Essential Medicines

Define Intervention, Prove efficacy & effectiveness, Define Product, Manufacture, Gain regulatory approval / endorsement, Initiate local coverage, Ensure local use

WHO Model List of Essential Medicines for Children

15. DISINFECTANTS AND ANTI SEPTICS
15.1 Antiseptics
- Chlorhexidine: Solution: 5% (digluconate), 20% (digluconate) (needs to be diluted prior to use for local care).
- Iodine: Solution: 5% (diformate).
- Polysyndone iodine: Solution: 10% (equivalent to 1% available iodine).

National List of Essential Medicines 2003

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Category</th>
<th>Route of Administration / Dosage Form</th>
<th>Strengths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorhexidine</td>
<td>U</td>
<td>Solution</td>
<td>5% (conc. for dilution)</td>
</tr>
<tr>
<td>Ethyl Alcohol 70%</td>
<td>U</td>
<td>Solution</td>
<td>20% (conc. for dilution)</td>
</tr>
</tbody>
</table>

3rd list (March 2011)

http://www.searo.who.int/LinkFiles/Essential_Drugs_and_Medicines_India.pdf
WHO’s stance on inclusion of 4% CHX is pending a commercially available product as used in the trials

From page 55 of The Unedited Report of 18th Expert Committee on the Selection and Use of Essential Medicines (21 to 25 March 2011):

“The problem remains that, as in 2009, a commercially available preparation of 7.1% chlorhexidine digluconate solution or gel (delivering 4% chlorhexidine) is not yet available. While the 20% requires dilution and manipulation and is clearly not optimal, until there is a commercially available product of the strength and formulation used in the trials, the current listing cannot be amended. However, the Committee noted that an optimized 4% chlorhexidine is listed as one of the priority products for development by WHO on the Priority Medicines list for maternal and child health and therefore flagged it as a ‘missing’ essential medicine, given the impact on mortality suggested in the trials.”

Source: The Unedited Report of 18th Expert Committee on the Selection and Use of Essential Medicines
Lomus has license from the Department of Drugs Authority of Nepal to market 4% CHX for Cord Care through July 2012

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These certificates are issued and re-issued periodically—Lomus maintains current registration and sales.
Lower concentration chlorhexidine for wound care is available as an over the counter generic around the world

| Define Intervention | Prove efficacy & effectiveness | Define Product | Manufacture | Gain regulatory approval / endorsement | Initiate local coverage | Ensure local use |

From a Kiosk in Delhi
From a drugstore in San Francisco

From a Kiosk in Delhi
From a drugstore in San Francisco
Community health workers and traditional birth attendants have both shown an ability to use CHX correctly

Define Intervention | Prove efficacy & effectiveness | Define Product | Manufacture | Gain regulatory approval / endorsement | Initiate local coverage | Ensure local use

Community Health Workers in Nepal

A four district pilot in Nepal has trained community health workers to administer chlorhexidine using dolls like the one above, and has shown correct usage at 47-67% of births in their catchment areas over one year

Traditional Birth Attendants in Pakistan

The 9741 birth Pakistan study relied on training of traditional birth attendants and caretakers to correctly administer chlorhexidine. The study reported a 38% reduction in mortality as a result.
CHX may not lend itself to private sector-only distribution, but some pharmacists stock gentian violet for cord care

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</table>

### Characteristic | Relevance
---|---
Low priced product | Low priced products are generally unattractive to retailers unless they are fast moving, “traffic building” products like soap or candy which trade in considerable volume
Infrequent purchase | Most Indian women have the need to purchase chlorhexidine about 4 times in their lives, making the product among the slowest moving in inventory
Customer education | Synovate focus groups in Uttar Pradesh show that pharmacists are generally not powerful influencers on newborn cord care. The impetus to seek CHX will need to come from another source

Typical medical shop of Uttar Pradesh
Community health workers have shown an ability to both win trust of mothers and use chlorhexidine correctly.

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</table>

Community health workers trained in Nepal

A Nepali community health volunteer demonstrates correct application technique on a training doll in Banke district.

High rates of correct use in the community over the first year

Correct CHX application in three Nepali districts (April 2010-March 2011)

<table>
<thead>
<tr>
<th>District</th>
<th>Correct Use Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banke</td>
<td>68% (n=402)</td>
</tr>
<tr>
<td>Jumla</td>
<td>77% (n=337)</td>
</tr>
<tr>
<td>Bajhang</td>
<td>70% (n=278)</td>
</tr>
</tbody>
</table>

Directly observed correct use refers to cases where:
- Caregiver applied a full tube of CHX
- Caregiver applied it in a single application
- CHX covered cord stump and surrounding areas
- CHX administered within 2 hours of cutting cord
ASHAs have a demonstrated effect on cord care practices in UP, boosting dry cord care 22%.

**Well-trained ASHAs can be significant drivers of cord care behavior change**

- Women who were contacted by an ASHA were 22% more likely to practice dry cord care relative to women who did not meet an ASHA during pregnancy.
- Other independent variables of caste, standard of living index, women's education, and mass media did not show significant influence.
- ASHA training could be improved to provide a clearer consensus on cord care practices.

**Source:** Varma et al. Increasing Postnatal Care Of Mothers And Newborns Including Follow-up Cord Care And Thermal Care In Rural Uttar Pradesh. J of Family Welfare. Vol 56 2010
ASHAs concentrate primarily on performance-linked payments, but none currently exists for cord care.

An incentive for cord care advice could accelerate cord care behavior change:

- Each state uses a different incentive schedule
- Incentives in the range of $0.50 to $2 appear to be significant motivators
- Proof of outcome may be challenging in this case, as there will be no medical record and empty sachets are insufficient
- ASHA behavior may be case identification and referral to ANM, which may be more easily verified
Sustaining supply requires profitable manufacture of this low volume product—companies can widen margins in at least 4 ways

1. **Price to take full advantage of willingness to pay**: Price changes of just a few pennies can dramatically shift profitability.

2. **Simplify packaging**: Current designs use a package insert and outer box which may contribute up to $0.05 in costs.

3. **Engage manufacturers with economies of scope**: Companies with existing CHX capacity may be able to produce at lower cost.

4. **Arrange procurement of a buffer stock if necessary**: If volume does not merit continuous production, purchase a large quantity and warehouse it for up to 2 years.

*A 3g tube will likely have the following cost structure (Estimated in USD)*

- **Somewhat Flexible**
- **Somewhat Fixed**

<table>
<thead>
<tr>
<th>Component</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHX</td>
<td>0.01</td>
</tr>
<tr>
<td>Packaging</td>
<td>0.09</td>
</tr>
<tr>
<td>SG&amp;A</td>
<td>0.07</td>
</tr>
<tr>
<td>CHX</td>
<td>0.13</td>
</tr>
<tr>
<td>Retail Price</td>
<td>0.33</td>
</tr>
</tbody>
</table>

**EBITDA** = Earnings before interest, taxes, depreciation, amortization

*Margins in the OTC retail channel are fixed at ~65% by an agreement of Industry Associations*

**Source:** Organization of Pharmaceutical Producers of India, 2011
Sustaining demand requires continuous effort to maintain awareness & promotion of the product from key influencers

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Most mothers in UP are aware of the risk of infection and wish to minimize it

“We apply mustard oil to the cord stump to prevent infection…

…if a trusted person recommends something else, we will use this new product”

Trusted influencers often include several key players acting on the mother-in-law, mother, and her peer group

- Formal Doctors
- ASHAs
- ANMs
- Informal Docs
- Other Informal Providers

Source: UP Consumer Research (photos of study respondents)