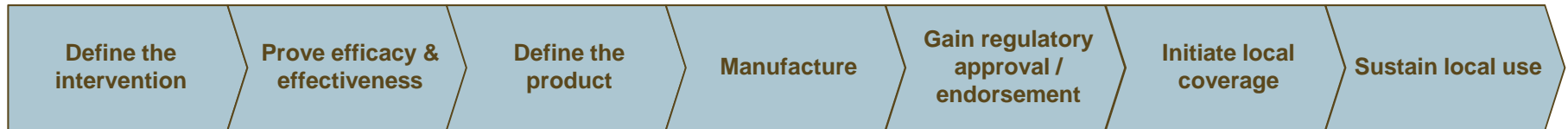




# **Chlorhexidine end-to-end analysis focusing on Uttar Pradesh**

**Prepared for Chlorhexidine Working Group  
December 2012  
Joel Segre**

# Background on Chlorhexidine (CHX)



Chlorhexidine as produced in Spain



Healthy cord at 7 days



Cord infection (omphalitis)



Chlorhexidine in Pakistan

## 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

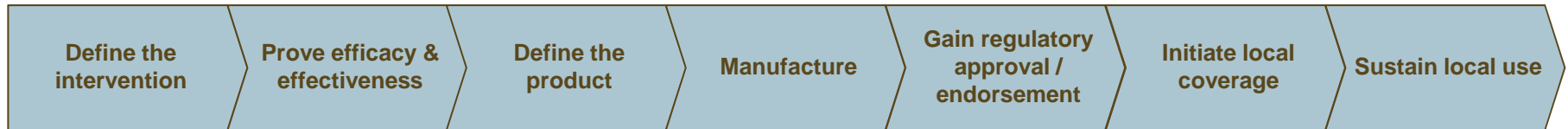
## Chlorhexidine for cord care

- 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

# There have been three large randomized controlled trials on 7.1% chlorhexidine gluconate for cord care in South Asia

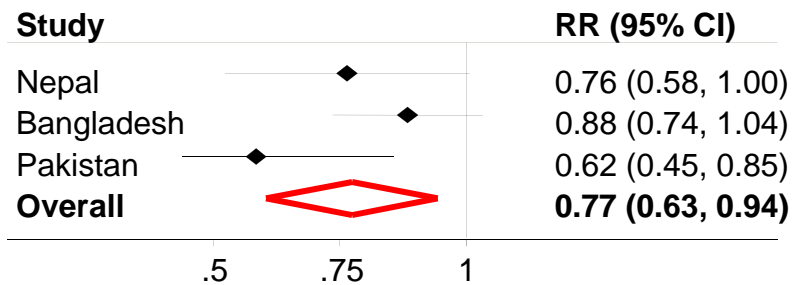
	Define the intervention	Prove efficacy & effectiveness	Define the product	Manufacture	Gain regulatory approval / endorsement	Initiate local coverage	Sustain local use
<b>Study Characteristic</b>			<b>Nepal</b>		<b>Bangladesh</b>		<b>Pakistan</b>
<b>Overall NMR</b> (at time of study)			30/1000		36/1000		30/1000
<b>% Home Births</b> (at time of study)			92%		88%		80%
<b>Sample Size Total</b>			15,123		29,760		9,741
<b>Primary Outcomes</b>			Mortality Omphalitis		Mortality Omphalitis		Mortality Omphalitis
<b>Comparison Group</b>			Dry Cord Care		Dry Cord Care		Dry Cord Care
<b>Freq of Multiple App</b>			1,2,3,4,6,8,10		1,2,3,4,5,6,7		Daily for 14 days
<b>Intervention provider</b>			Project staff		Project staff		TBA & Caretaker

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



## Neonatal mortality: 23% reduction

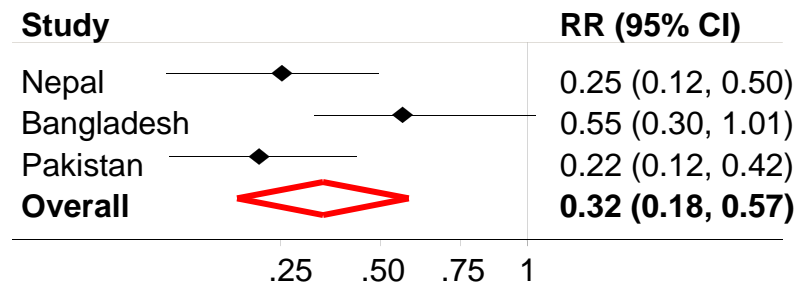
### Mortality in CHX vs. No CHX groups



- 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

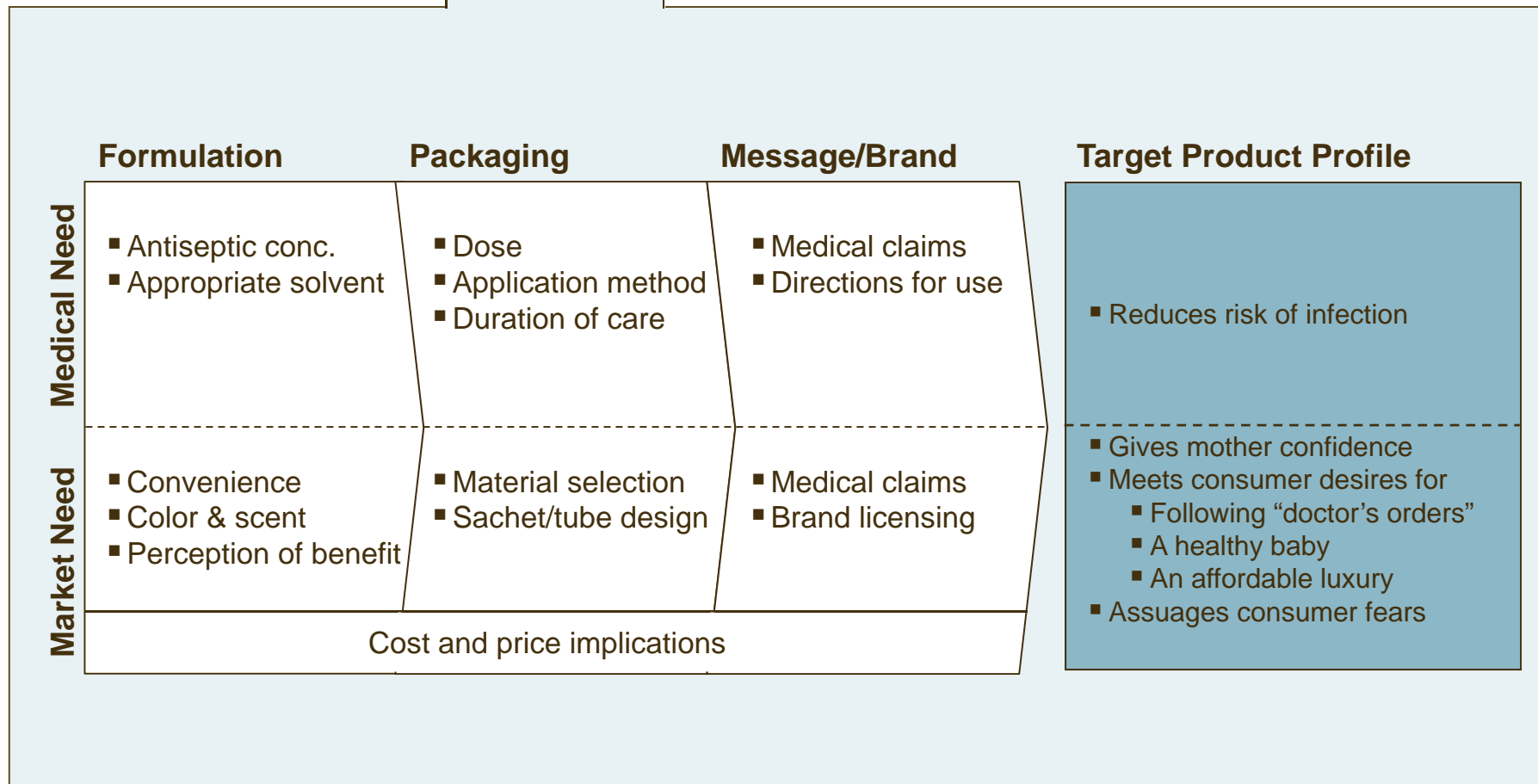
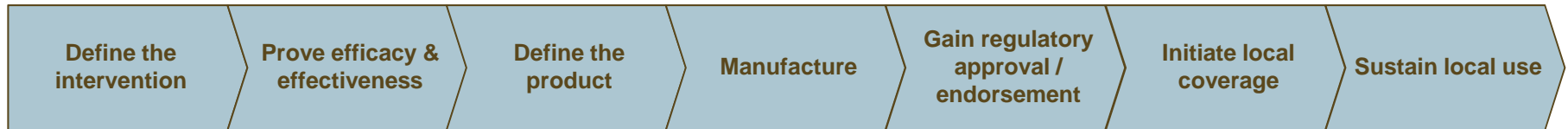
## Severe infection: 68% reduction

### Severe Infection in CHX vs. No CHX groups

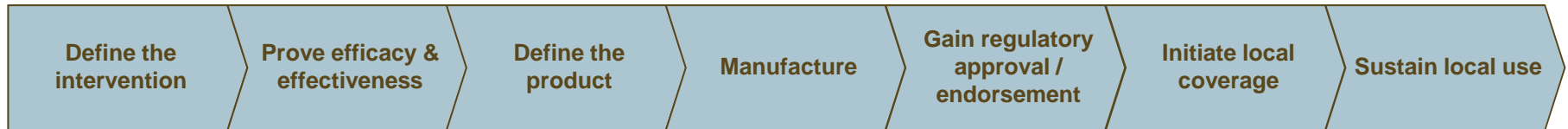


- Reduction in severe cord infections are correlated with repeat application of chlorhexidine
- Incidence of visible cord infection and mortality do not appear correlated

# 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

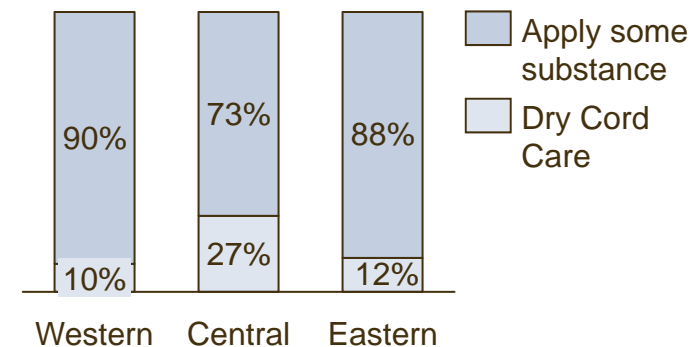


**Most mothers in UP are aware of the risk of infection and wish to minimize it**

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



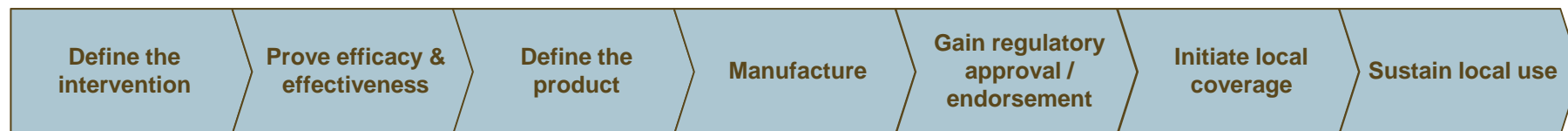
**Across the state, 83% of mothers apply some substance to the cord stump (n=4472)**



Commonly applied substances include:

- Mustard Oil (46% of respondents)
- Ghee
- Turmeric
- Linseed oil
- Powders & ointments (next page)

# Without a specific product for cord care, some mothers seek medicines associated with infection prevention and treatment



## Re-purposing of other medicines for umbilical cord care

Photo as presented in village



Product	Chloromycetin	Neosporin	Gentian Violet
Price	Rs. 50 (1/caplet)	Rs. 22	Rs. 5
Community uses	Umbilical care Eye infections	Wound Care Umbilical care	Umbilical care
Location	Uttar Pradesh	Uttar Pradesh	Bihar

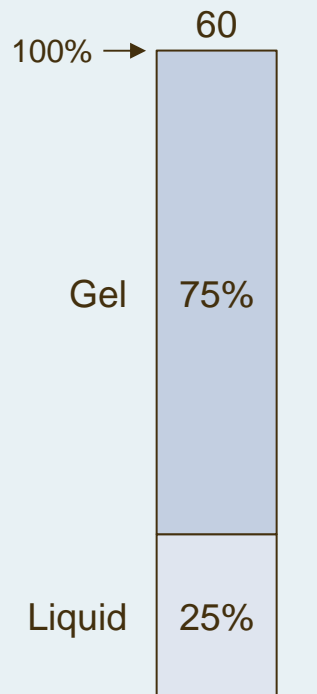
## In-Community Comparables

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

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



## Nepali Formulation Preferences



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.

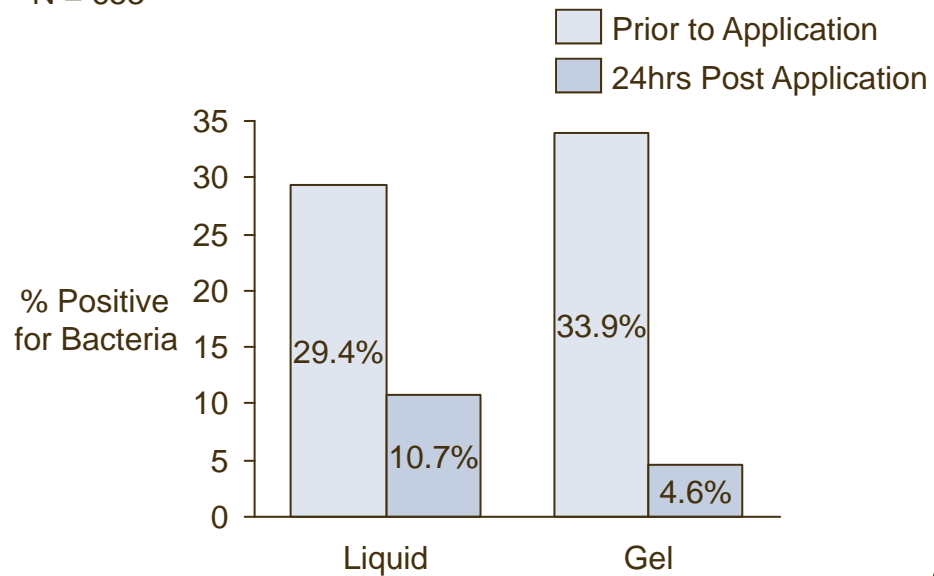


# Gel has proven to be as effective as (and possibly more effective than) liquid formulations of chlorhexidine



## Liquid and gel antiseptic performance

N = 653



## 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



# Formulation, instructions for use, and retail packaging must all be designed to fit the target population



## 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

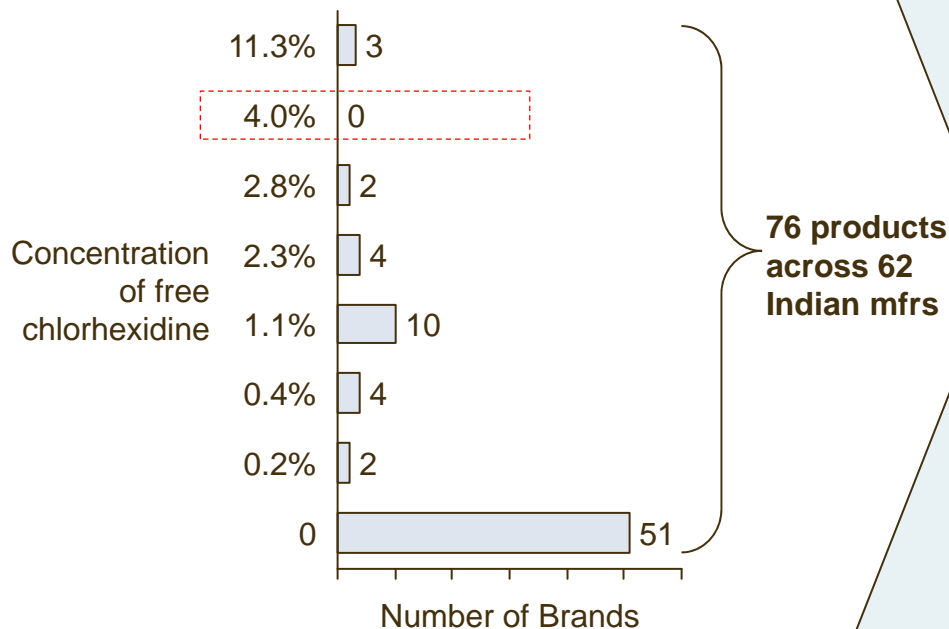


The name “Kawach” means “Shield”. Packaging in a collapsible tube and box conveys a medicinal product, although sachet packaging would have been less expensive

# There are at least 10 suppliers of CHX concentrate and 61 suppliers of finished CHX products in India alone



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



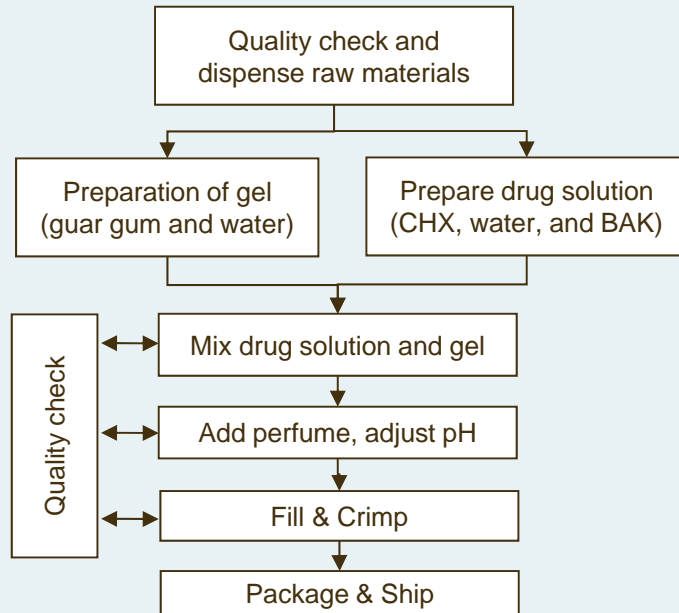
**There is no shortage of CHX manufacturing capacity in India**

- 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

# Manufacturing of chlorhexidine is a commoditized process using readily available techniques and equipment



## Manufacturing Process



## Manufacturing Equipment



Mixing equipment used to produce CHX gel at Lomus



Tube filling equipment used to produce CHX product at Lomus

# Ingredients of chlorhexidine gel are inexpensive; packaging and overheads drive manufacturing costs



## Product Cost Components

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

+

Packaging Component	Per Unit	Source
Pre-printed collapsible aluminum tube	\$0.04	Pefect Tubes Pvt
Printed paperboard box	\$0.04	Lomus Pharma Pvt
Printed color package insert	\$0.01	Lomus Pharma Pvt
<b>Total</b>	<b>\$0.09</b>	

+

Other	Per Unit	Source
Staff, Plant & Equipment, QC, Overheads, Profit	\$0.05-0.15	Lomus Pharma Pvt

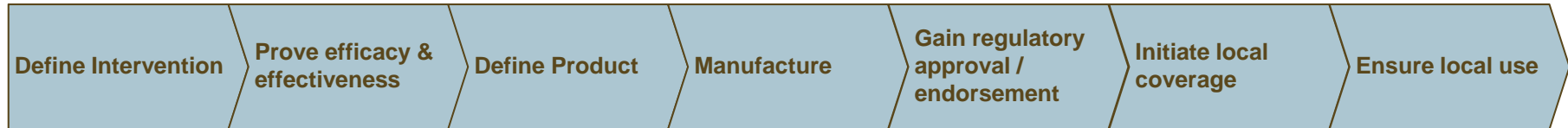
## Target Cost

\$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”



## WHO's cord care recommendations support CHX

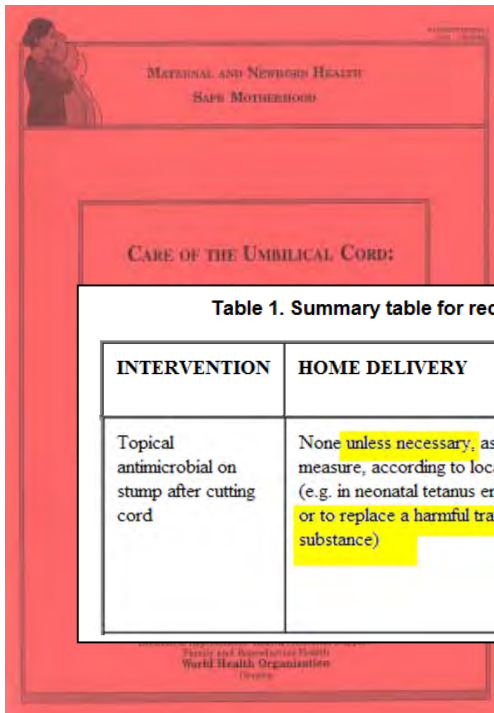


Table 1. Summary table for recommendations on cord care

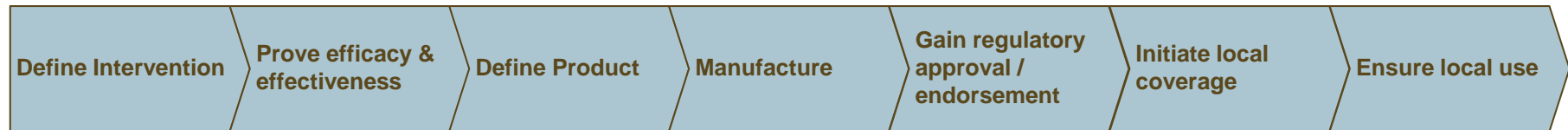
INTERVENTION	HOME DELIVERY	INSTITUTIONAL DELIVERY
Topical antimicrobial on stump after cutting cord	None unless necessary, as a temporary measure, according to local situation (e.g. in neonatal tetanus endemic areas, or to replace a harmful traditional substance)	24-hour rooming-in: none unless necessary, according to local situation  Nurseries/intensive care units: chlorhexidine, tincture of iodine, povidone-iodine, triple dye or silver sulphadiazine

### 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**

# CHX 5% is on the WHO Essential Medicines List for Children and India's National List of Essential Medicines



## WHO Model List of Essential Medicines for Children

15. DISINFECTANTS AND ANTISEPTICS	
15.1 Antiseptics	
<input type="checkbox"/> chlorhexidine	Solution: 5% (digluconate); 20% (digluconate) (needs to be diluted prior to use for cord care).
<input type="checkbox"/> ethanol	Solution: 70% (denatured).
<input type="checkbox"/> polyvidone iodine	Solution: 10% (equivalent to 1% available iodine).

3rd list  
(March 2011)

## National List of Essential Medicines 2003

NATIONAL LIST OF ESSENTIAL MEDICINES 2003			
Medicine	Category	Route of Administration/ Dosage Form	Strengths
Cetrimide	U	Solution	20% (conc. for dilution)
Chlorhexidine	U	Solution	5% (conc. for dilution)
Ethyl Alcohol 70%	U	Solution	



Directorate General of Health Services  
Ministry of Health & Family Welfare  
Government of India



# WHO's stance on inclusion of 4% CHX is pending a commercially available product as used in the trials



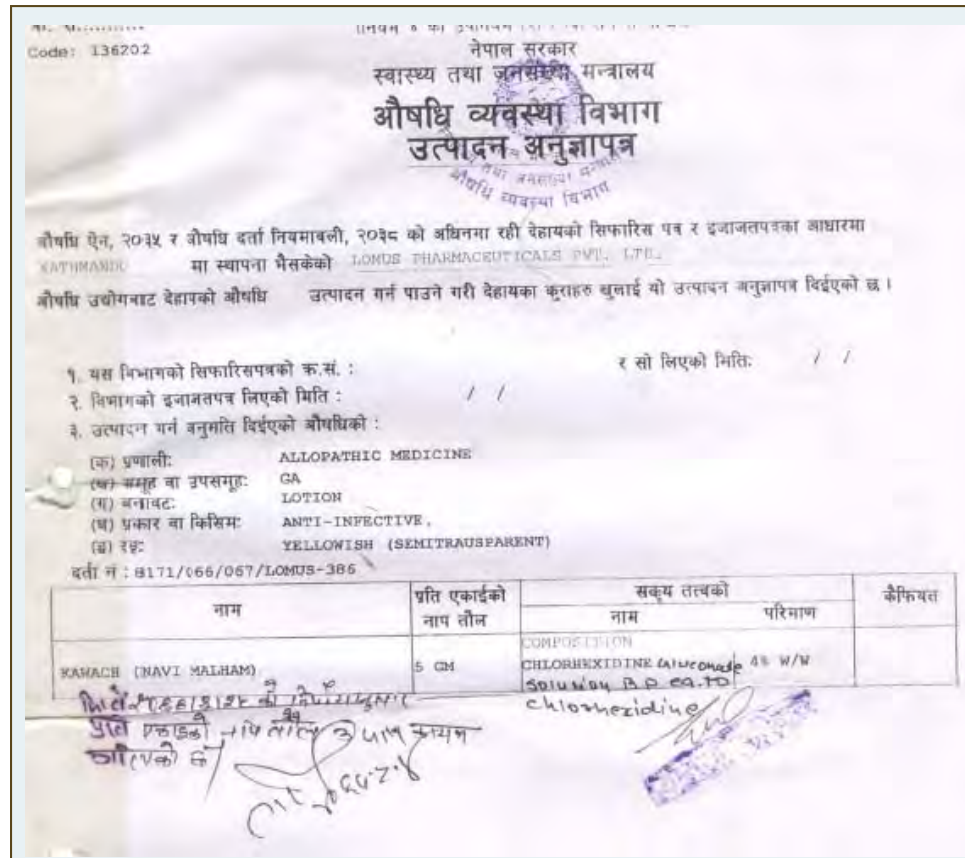
From page 55 of The Unedited Report of 18th Expert Committee on the Selection and Use of Essential Medicines (21 to 25 March 2011):

“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.”

**A new application for inclusion was submitted to the WHO in December 2012 for consideration in the 19<sup>th</sup> 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



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



From a drugstore in San Francisco



From a Kiosk in Delhi

# Community health workers and traditional birth attendants have both shown an ability to use CHX correctly



## 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



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



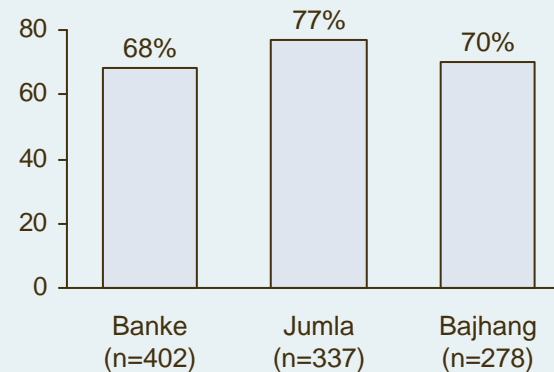
## Community health workers trained in Nepal



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)



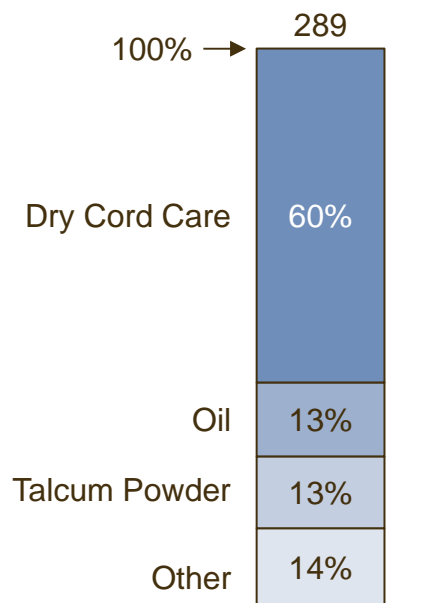
Directly observed correct use refers to cases where:

- 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%



**ASHAs have not quite reached a consensus for cord care in rural UP**



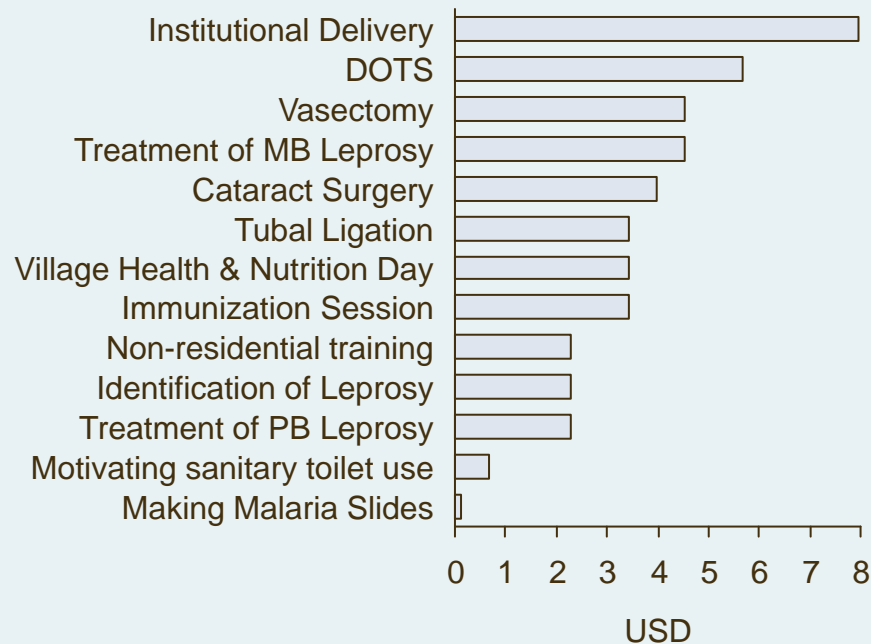
**Well-trained ASHAs can be significant drivers of cord care behavior change**

- 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

# ASHAs concentrate primarily on performance-linked payments, but none currently exists for cord care



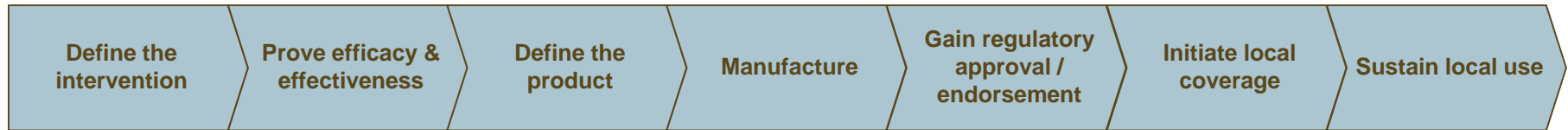
## ASHA Incentive Schedule



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

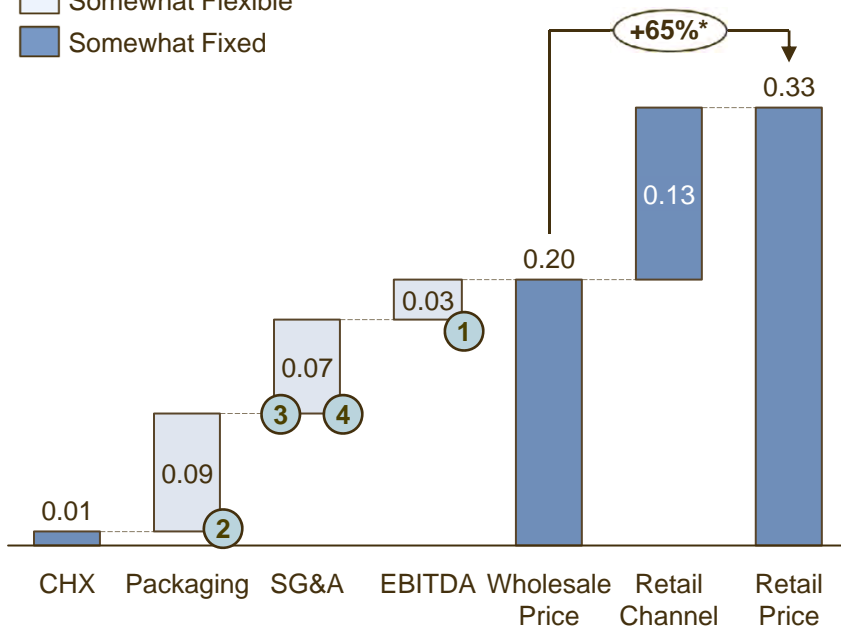
- Each state uses a different incentive schedule
- Incentives in the range of \$0.50 to \$2 appear to be significant motivators
- Proof of outcome may be challenging in this case, as there will be no medical record and empty sachets are insufficient
- ASHA behavior may be case identification and referral 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



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

- Somewhat Flexible
- Somewhat Fixed



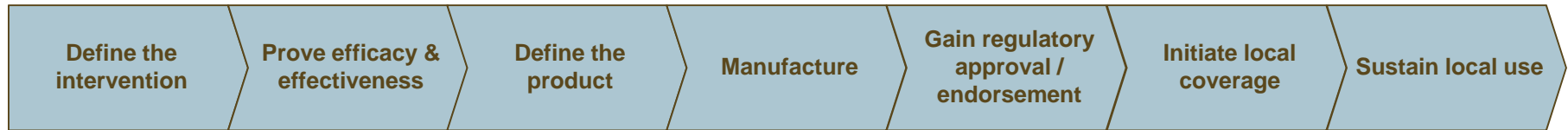
## There are at least 4 ways to widen margins

- 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

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



# Sustaining demand requires continuous effort to maintain awareness & promotion of the product from key influencers



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