

# Increasing the Use of Dexamethasone in the Management of Preterm Birth in Cambodia

## INTRODUCTION

Preterm birth is defined as a live birth before 37 completed weeks of pregnancy. While a preterm infant's likelihood of survival has improved over the years, there is still a high rate of mortality and serious morbidity associated with prematurity. In Cambodia the preterm birth rate is 10.5% according to the 2012 *Born Too Soon* report,<sup>1</sup> and the Ministry of Health has identified prematurity as a priority issue to reduce newborn mortality and improve newborn health.

The national Safe Motherhood Clinical Management Protocols of National Maternal Child Health Center (NMCHC) and the Ministry of Health (MoH) provide basic guidance on the management of women at risk of imminent preterm birth and care of the preterm newborn. These guidelines include the administration of dexamethasone to women at risk of imminent preterm birth in order to help reduce the complications that newborns may experience due to prematurity. Antenatal corticosteroid (ACS) administration is recommended for women with preterm labor, preterm prelabor rupture of membranes and for women who are preterm and experience obstetrical complications which could necessitate delivery, such as severe pre-eclampsia/eclampsia or antepartum hemorrhage.



**Figure 1. Map of Cambodia with location of study sites. Note that there are two sites in Phnom Penh.**

**Table 1. Key Indicators for Cambodia**

INDICATOR*	VALUE
Total Population [a]	14,865,000
Annual number of births [b]	386,451
Maternal Mortality Ratio (maternal deaths per 100,000 live births) [c]	206
Neonatal Mortality Rate (neonatal deaths per 1,000 live births) [c]	27
% of pregnant women receiving at least 1 ANC visit [c]	89%
% of pregnant women receiving at least 4 ANC visits [c]	59%
% of deliveries in a facility [c]	54%
% of deliveries with a skilled birth attendant [c]	71%
% of births that are preterm [d]	10.5%

Sources:

[a] WHO. (2013). Global health observatory data repository, Western Pacific Region: Cambodia statistics summary (2002-present) [database]. Retrieved from <http://apps.who.int/gho/data/node.country.country-KHM?lang=en>.

[b] WHO. (2012). Cambodia: Neonatal and Child Health Profile [database]. Retrieved from [http://www.who.int/maternal\\_child\\_adolescent/epidemiology/profiles/neonatal\\_child/khm.pdf](http://www.who.int/maternal_child_adolescent/epidemiology/profiles/neonatal_child/khm.pdf).

[c] National Institute of Statistics, Directorate General for Health, and ICF Macro, 2011. Cambodia Demographic and Health Survey 2010. Phnom Penh, Cambodia and Calverton, Maryland, USA: National Institute of Statistics, Directorate General for Health, and ICF Macro. Retrieved from <http://dhsprogram.com/pubs/pdf/FR249/FR249.pdf>.

[d] March of Dimes, PMNCH, Save the Children, WHO. (2012). *Born Too Soon: The Global Action Report on Preterm Birth*. (Wall Chart: Estimated National Rates of Preterm Birth in 2010). Eds Howson, CP, Kinney, MV, Lawn, JE. Geneva: World Health Organization. Retrieved from <http://www.marchofdimes.com/materials/born-too-soon-the-global-action-report-on-preterm-birth-wallchart.pdf>.

Corticosteroids, of which dexamethasone is a common example, are a class of drugs that trigger fetal synthesis of proteins that make surfactant in the lungs and also have a protective effect on cerebral blood vessels and the intestines.<sup>2</sup> A Cochrane review concluded that antenatal corticosteroid use before preterm birth was associated with a 34% reduction in respiratory distress syndrome, a 46% reduction in

intracranial hemorrhage, a 54% reduction in necrotizing enterocolitis, and a 31% reduction in neonatal death.<sup>2</sup> The review also concluded that ACS administration before preterm birth is not associated with any adverse effects for the delivering mother. New clinical recommendations from the World Health Organization (WHO), to be released in late 2014, confirm these practices. The impact on neonatal mortality in low- and middle-income countries could be greater, approaching 50%.<sup>3</sup>

## Demographic Situation for Cambodia

Cambodia has a total population of approximately 14,865,000 people (Table 1).<sup>4</sup> Just over half (54%) of all births in Cambodia occur in facilities, and 59% of pregnant women receive at least four antenatal care visits.<sup>5</sup> The maternal mortality ratio is 206 maternal deaths per 100,000 live births, while the neonatal mortality rate is 27 neonatal deaths per 1,000 live births.<sup>6</sup>

## METHODS AND IMPLEMENTATION

The objective of this study was to improve the quality of care provided to pregnant women at risk of imminent preterm birth by increasing the rate of administration of dexamethasone in order to prevent complications of prematurity among preterm newborns. This was done through provision of up-to-date technical information about prematurity and the use of dexamethasone, regular technical support through performance audits and periodic feedback based on those audit data.

The study was implemented under the direction of NMCHC/MoH Cambodia and the existing Sub-Technical Working Group on Maternal Child Health. The local research was managed by Human Development Research Cambodia (HDRC), which met regularly with the NMCHC and engaged directly with the six research sites. Overall technical guidance for the research was provided by the USAID-funded Maternal and Child Health Integrated Program (MCHIP).

The study took place in six public facilities widely distributed across Cambodia (Table 2). Facilities were purposely selected as facilities with high delivery volume but also representative of different levels of the Cambodian health system. Study implementation was from November 2013 to May 2014. Final endline data were collected in June of 2014.

**Table 2. Key Facility Indicators at Baseline (October 2013)**

FACILITY NUMBER	FACILITY NAME	CITY	NUMBER OF BIRTHS PER MONTH	PRETERM BIRTH RATE
1	National Maternity Child Health Center Hospital	Phnom Penh	685	12.0%
2	Municipal Referral Hospital	Phnom Penh	180	3.9%
3	Battambang Referral Hospital	Battambang	292	7.9%
4	Siem Reap Referral Hospital	Siem Reap	159	4.4%
5	Takeo Referral Hospital	Takeo	151	28.5%
6	Kampong Cham Referral Hospital	Kampong Cham	159	6.3%

A facility-level assessment was conducted at the beginning and end of the intervention, and consisted of a facility readiness review, commodity assessment and barriers analysis. This included the verification of availability and storage conditions of medications, supplies, equipment, staffing, record keeping and infrastructure related to maternal and newborn health at each of the sampled facilities. Knowledge and confidence of a sample of health care providers related to screening, management and treatment pertaining to ACS administration were measured before and after the intervention at each facility. In-depth interviews of key informants who either made decisions or influenced decision making or policy related to maternal and newborn health in the country were conducted at the start and end of the intervention to identify the prevailing issues related to their professional experience and personal opinions regarding service provision for women with high probability of preterm birth and how changes either supported or limited the identification and proper management of preterm births. In addition, treatment practices were measured through chart review on a monthly basis to identify those women at risk of imminent preterm birth, and their clinical management. The tools are all available with the MCHIP office in Washington, DC.

Best practice in this situation was defined as follows, based on the Cambodia Safe Motherhood Clinical Management Protocols and WHO clinical recommendations available at the time of the study design:

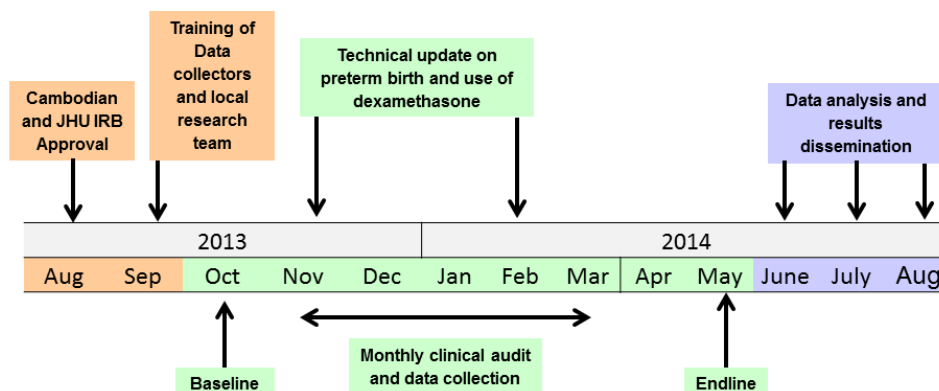
- Women with a condition that increased the probability of imminent preterm birth (i.e., preterm labor, preterm prelabor rupture of membranes, antepartum hemorrhage or severe pre-eclampsia/eclampsia) would be adequately identified by the providers;
- Gestational age would be assessed as accurately as possible;
- Women estimated to be between 24+0 and 36+6 weeks gestation, with an above-mentioned condition, would be given a course of dexamethasone (24mg in divided doses) for prevention of complications of prematurity among the newborns born preterm.

The study was approved by the National Ethics Committee for Health Research of the MoH/Cambodia and the Institutional Review Board of The Johns Hopkins Bloomberg School of Public Health.

## Timeline

The program was undertaken according to the timeline below (Figure 2). Preparation and training took place during the months of August and September 2013. The baseline occurred in all six facilities in October 2013, and was followed by a technical update to clinical staff on site by the local study coordinators in November 2013. The technical update focused on identification of clinical conditions which increase the risk of imminent preterm birth, accurate and precise estimation of gestational age, and use of dexamethasone, including correct administration and benefits. Data collection and facility-level audit and feedback occurred monthly from November 2013 to April 2014, with the endline in May 2014. The results were presented at a national dissemination meeting in Phnom Penh in July 2014.

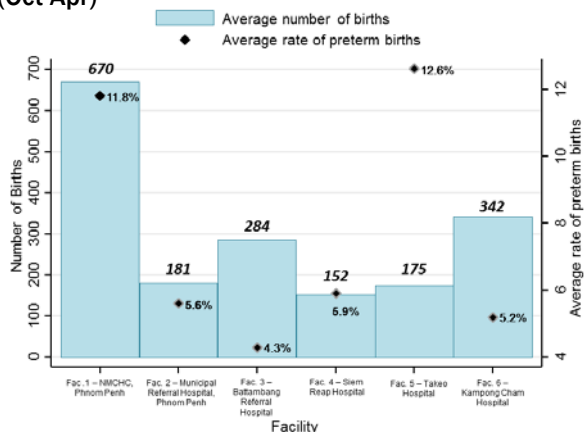
Figure 2. Program Timeline



## Facility Volume and Preterm Birth Rates

The average number of total births and the proportion of preterm births varied widely between the six facilities included in the study (Figure 3). The average number of monthly births ranged from 670 (NMCHC) to 152 (Siem Reap), while the rate of preterm birth ranged from 4.3% (Battambang) to 12.6% (Takeo).

Figure 3. Average Number of Births and Average Preterm Birth Rate During Intervention by Facility (Oct-Apr)

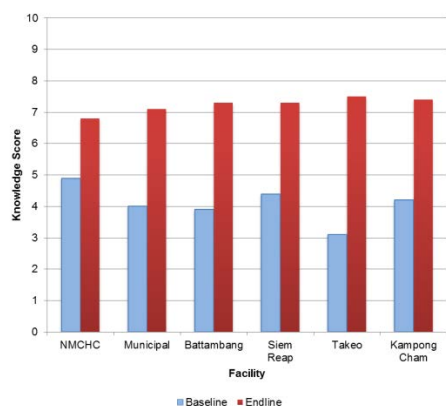


## FINDINGS AND DISCUSSION

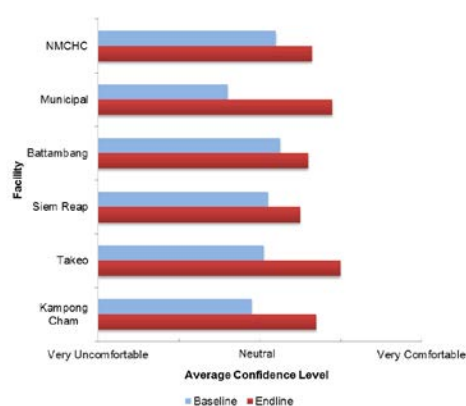
### Health Worker Knowledge and Confidence

Knowledge of prematurity and the correct use of dexamethasone increased substantially across all six facilities from baseline to endline (Figure 4). At baseline, the average knowledge score of health providers interviewed at all facilities was five or lower (out of a possible nine points), but scores at all facilities increased to approximately seven at endline. Health provider confidence in appropriate administration of dexamethasone under a wide range of clinical situations also increased across all facilities from baseline to endline (Figure 5).

**Figure 4. Knowledge Score at Baseline and Endline, by Facility**



**Figure 5. Confidence Level at Baseline and Endline, by Facility**



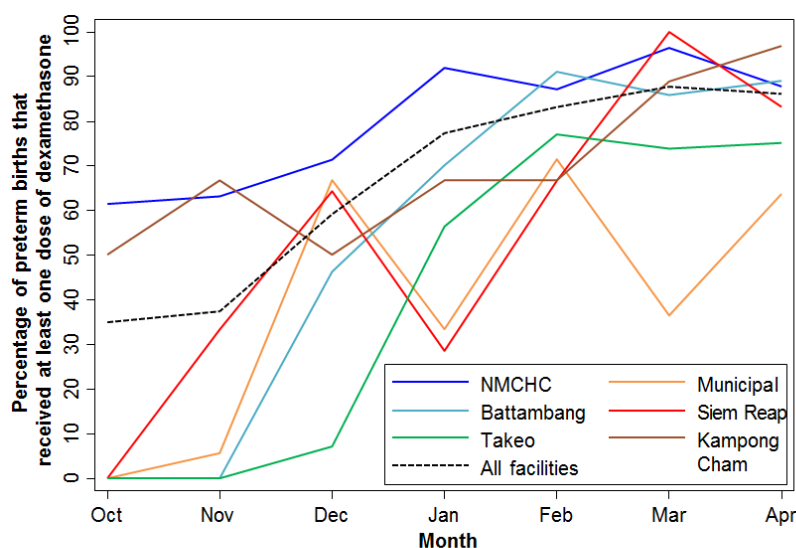
### Coverage of Dexamethasone

At baseline, provision of dexamethasone to women at risk of imminent preterm birth was practiced at two of the six study facilities. Precise gestational age calculation was not a standard practice in any of the facilities. Most providers at all facilities were unclear about the national ACS treatment guidelines.

The greatest net change was measured at Siem Reap, where no preterm births received ACS at baseline and 83% received ACS at endline; similarly, Takeo increased from 0% to 75% (Figure 6). NMCHC achieved coverage above or near 90% during several months.

Battambang had coverage rates of 86%-91% during the last three months of the study. At the Municipal hospital, progress was uneven, and maternity ward directors reported that many women arrived at the hospital in advanced labor, and providers reported that they did not have enough time to administer the drug. Overall, the trend was for increased indicated use of dexamethasone, from a baseline of 34.9% to 86.1% at endline.

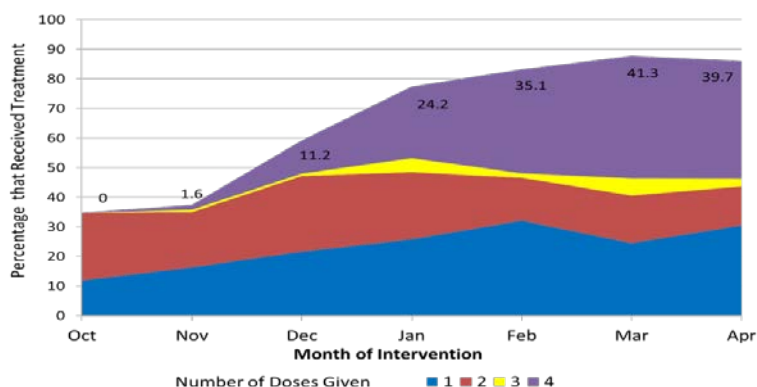
**Figure 6. Percentage of Preterm Births that Received at Least One Dose of Dexamethasone, by Facility and Month**



Average percentage use of dexamethasone, by month, all facilities						
Oct	Nov	Dec	Jan	Feb	Mar	Apr
34.9	37.4	59.2	77.3	83.2	87.7	86.1

At baseline, women who received ACS were only given one to two doses of 12mg each.\* By endline, 40 percent of women received four doses, the number recommended during the technical update (Figure 7). The most common reason identified for incomplete course was that the patient delivered before the full course could be given. This change should be viewed with caution, given the global change in recommendations. For ease of use, the current recommendation is for women to receive two doses of 12mg each, 12 or 24 hours apart.

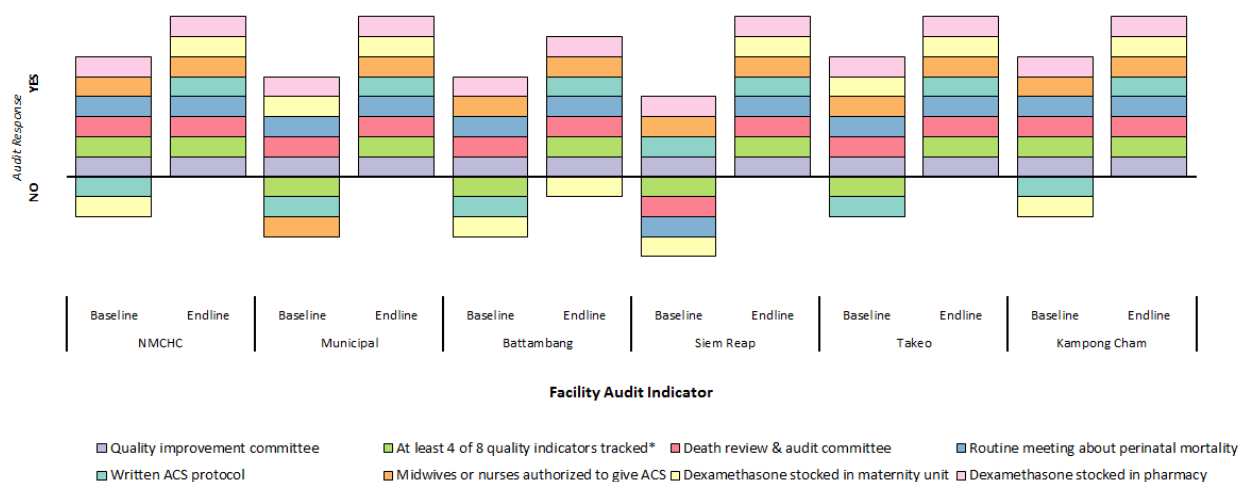
**Figure 7. Proportional Distribution of Doses of Dexamethasone Given, among all Women at Risk of Preterm Birth for all Facilities Combined, by Month**



### Facility Readiness and Commodity Assessment

Though starting from relatively high scores at baseline, further increases in the facility-level scores on readiness and commodity assessment were measured at endline. All six facilities reported the existence of a quality improvement committee (Figure 8). The number of facilities that reported tracking at least four quality indicators (out of a maximum of eight) increased from two at baseline to all six at endline. At baseline, all except one (Siem Reap) had a death review and audit committee that routinely met to discuss perinatal mortality, and midwives or nurses were authorized to administer ACS in all except one facility (Municipal); by endline, all facilities reported the existence of a death review and audit committee, and authorization of midwives or nurse to administer ACS (a provision already authorized in the national policy). Interestingly, only one facility (Siem Reap) had the ACS protocol available during the baseline visit, while all six facilities had the protocol available at endline. All facilities stored dexamethasone in the pharmacy at both baseline and endline; however, the number of facilities storing it in the maternity unit increased from two to five between baseline and endline assessments. It is likely that a component of the improvement in the management of preterm births was due to increased facility readiness and commodity availability between baseline and endline.

**Figure 8. Facility Audit Data at Endline and Baseline**



\* The 8 quality indicators were: cleanliness of reception areas; cleanliness of hospital grounds; availability of secure record room for storing inpatient medical records; reliability of the main source of electricity; presence of working generator for alternative power source; reliability of hospital's main water source; total number of beds in the maternity ward/unit in facility; and type of delivery area.

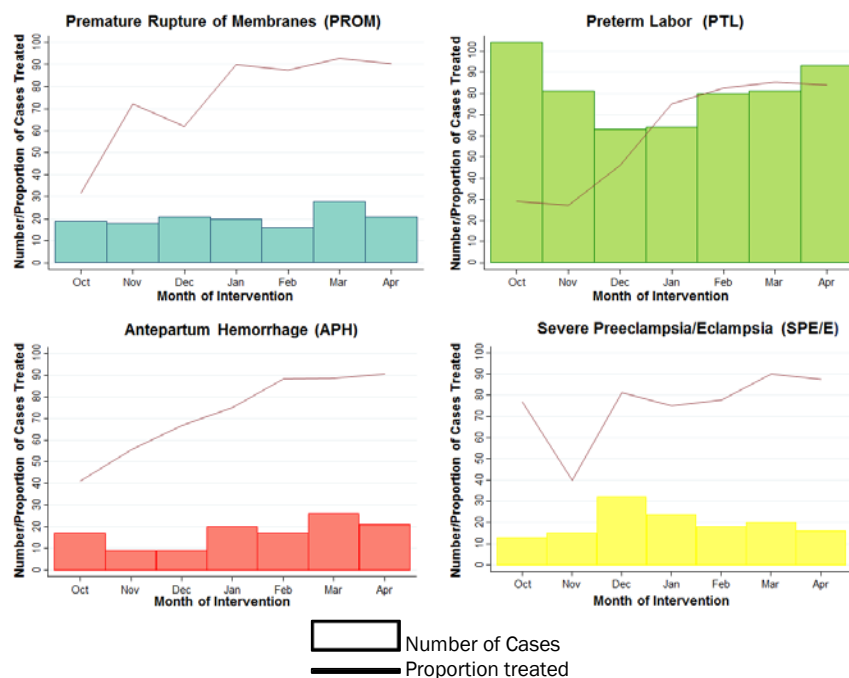
\* At the start of the study, global recommendations for dexamethasone administration were to give 6mg every 12hours for four doses. In April 2014 at a meeting convened by WHO in Geneva, the recommendation was modified to allow 12mg every 24hours for two doses.



## Preterm Birth Audit Data

The proportion of pregnant women receiving 24 mg of dexamethasone (in divided doses) between 24 +0 and 36 +6 weeks of gestation increased over the duration of the study across all four conditions associated with increased probability of imminent preterm birth (Figure 9). Pregnant women presenting with preterm labor constituted the largest proportion among the four conditions presenting at the six study facilities. Interestingly, the number of women identified with any of the four clinical conditions did not increase over time. It was expected that the increase in the awareness of preterm birth would increase the number of women considered eligible. Instead, the increases in utilization were due to improved provision to women who were identified as at risk of imminent preterm birth. The unstable rate for the proportion of SPE/E cases treated can be attributed to the small total number of cases—less than 30 per month divided among six facilities.

Figure 9. Number of Cases and Proportion Treated with ACS, by Diagnosis (Aggregate Data for all Facilities)

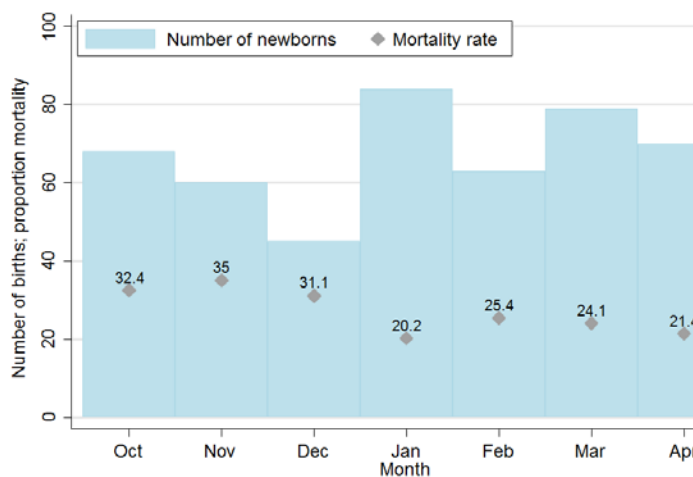


The number of preterm newborns admitted to the special care nursery in the six study facilities ranged from a low of 48 (December 2013) to a high of 85 (January 2014) (Figure 10). Within this group of preterm newborns, the mortality rate appears to have decreased over the duration of this study. While the study was not designed to measure a statistically significant change in the mortality rate among preterm newborns, the decreasing trend does point towards an encouraging finding.

## Perspectives from Maternity Ward Directors and Other Managers

The study team conducted key informant interviews to obtain contextual information about ACS use at the facilities, at baseline (n=8) and endline (n=7). Notes from audit and feedback sessions were also compiled and analyzed qualitatively.

Figure 10: Number of preterm births admitted to special care nursery and mortality rate, by month



At baseline, six out of eight respondents said that the primary barriers to ACS use for preterm birth included limited technical capacity by birth attendants and existing policies. Five out of eight also said that facility usage patterns, such as women arriving to the hospital too late to receive treatment, were an important problem. Another concern was that gestational age calculation was not done universally, either because women were unable to report the date of their last menstrual period, or providers did not routinely record this information. Half of respondents did not know that a national policy for ACS existed, while the other half knew of its existence but were unclear on policy contents or wanted more detailed guidelines. Provision of clear guidelines was seen as a necessary first step to improving treatment rates. The cost of dexamethasone was not reported to be a limiting factor, as it is cheap and patients incur no extra cost for it. However, in some cases, the time required to obtain the medication was a limiting factor.

During the intervention, respondents indicated that graphs of hospital-level ACS results were displayed in various settings, with some hospitals displaying the graphs at meetings, while others posted them in the delivery rooms or staff rooms. All informants said that their facility had received some job aids and posters related to ACS use. Several key informants mentioned that they had received pregnancy wheels and noted that these were useful in their facility's improved calculation of gestational age. At several facilities, informants said that maintaining a whiteboard with a list of high-risk patients was an important aspect of the intervention.

At endline, informants noted an improvement in gestational age calculation and in providers' awareness of the need to provide timely treatment with ACS. While hospital-level stockouts were not reported to be a problem, three respondents said that increased attention was still needed to ensure that dexamethasone continued to be stored in the maternity units. Factors limiting the coverage of ACS included women arriving at the facility too late to receive treatment, and problems with medical record-keeping. All respondents indicated that they expected their staff to continue administering ACS even after the audit and feedback process ended.

Recommendations for future activities include: translating the ACS posters into Khmer, dissemination of ACS-related training to lower-level facilities and community-level providers, and continuing to discuss ACS at technical meetings.

### **Case Study: Successful Gains at the NMCHC Hospital, Phnom Penh**

The core elements of the intervention included a technical update followed by monthly audit of the preterm birth rates and provision of dexamethasone. Using that information the local research team held a monthly feedback call with the head of the clinical team at NMCHC to identify challenges, correct misconceptions and reinforce good practices. In response to the information obtained, each facility took a slightly different course of action. For example, at National Maternity Child Healthcare Hospital in Phnom Penh, where ACS coverage increased from about 60% to 90% during the intervention, facility leaders implemented several strategies to improve treatment rates. On two occasions, hospital leaders conducted a two-day technical update on antenatal corticosteroids, and all maternity unit staff participated. In addition, morning meetings for medical staff and care providers to handover patients included routine discussion on the use of ACS/dexamethasone for preterm birth. This message was reiterated at the Friday meetings for the medical staff. Medical record-keeping improved during the intervention, with midwives recording the use of dexamethasone (dose, number, and timing of doses) and noting the time for next dose. The maternity unit began to record the administration of dexamethasone on the whiteboard used to track high-risk patients. Finally, results regarding management of prematurity and use of dexamethasone were presented at monthly and quarterly meetings of the hospital's Technical Steering Committee.

## **KEY LESSONS LEARNED AND ACTIONS TO BE CONSIDERED**

- At baseline, providers were aware of the use of antenatal corticosteroids for preterm birth, but coverage was limited by unclear guidelines regarding indications and contraindications, dosage and timing of doses.
- A simple, focused intervention was able to improve coverage rates substantially in a short time period.
- Whereas a shortage of essential commodities can limit the provision of some life-saving maternal and neonatal interventions, this was not the case for dexamethasone. It was widely available in the six Cambodian hospitals studied and relatively affordable.
- At all facilities at endline, nurses and midwives, as well as physicians, were permitted to administer the drug.

- While not a direct component of this operations research study, the program resulted in improved accuracy and completeness of medical records at the facilities studied. This is likely due to the understanding that accurate reporting of achievement required complete and accurate documentation.
- While presence of adequate stock of dexamethasone in the pharmacy is necessary, ensuring adequate stock of dexamethasone in the maternity wards/units as well is essential to ensure drug availability at the point of use. This improved during the intervention and should continue.
- Further technical supervision should be continued to ensure there is no confusion about the correct regimen of dexamethasone (12mg IM, given either 12 or 24 hours apart, for total two doses), given the change in recommendations from the beginning to the end of the study.
- Given the simplicity of the intervention, continued supervision and support to these facilities by the hospital directors and chief obstetrical and nursing officers may be sufficient. The Ministry of Health and the NMCHC may be able to facilitate this through quarterly reporting of some of the indicators in the study.
- In order to expand the program to other facilities in the country, the MOH/NMCHC should develop an expansion plan that could use the expertise developed in the original six facilities.
- Further addressing the complications of preterm birth will require implementation of additional interventions, including improved diagnosis, better gestational age assessment, and administration of antibiotics, magnesium sulphate and better care for the preterm newborn, including use of kangaroo mother care and continuous positive airway pressure.

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<sup>1</sup> March of Dimes, PMNCH, Save the Children, World Health Organization [WHO]. (2012). Born Too Soon: The Global Action Report on Preterm Birth. (Wall Chart: Estimated National Rates of Preterm Birth in 2010). Eds Howson, CP, Kinney, MV, Lawn, JE. Geneva: World Health Organization. Retrieved from <http://www.marchofdimes.com/materials/born-too-soon-the-global-action-report-on-preterm-birth-wallchart.pdf>.

<sup>2</sup> Roberts, D., & Dalziel, S. (2006). Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*, 3(3).

<sup>3</sup> Mwansa-Kambafwile, J., Cousens, S., Hansen, T., & Lawn, J. E. (2010). Antenatal steroids in preterm labour for the prevention of neonatal deaths due to complications of preterm birth. *International journal of epidemiology*, 39(suppl 1), i122-i133.

<sup>4</sup> World Health Organization. (2013). Global health observatory data repository, Western Pacific Region: Cambodia statistics summary (2002-present) [database]. Retrieved from <http://apps.who.int/gho/data/node.country.country-KHM?lang=en>.

<sup>5</sup> National Institute of Statistics, Directorate General for Health, and ICF Macro, 2011. Cambodia Demographic and Health Survey 2010 [Cambodia DHS 2010]. Phnom Penh, Cambodia and Calverton, Maryland, USA: National Institute of Statistics, Directorate General for Health, and ICF Macro. Retrieved from <http://dhsprogram.com/pubs/pdf/FR249/FR249.pdf>.

<sup>6</sup> Cambodia DHS 2010.