Reducing Postpartum Hemorrhage in Thanh Hoa, Viet Nam

Assessing the Role of Active Management of Third Stage of Labor and of Oxytocin in Ampoules and Uniject Devices

Research Report

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PATH
A catalyst for global health

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* Uniject⊗ is a trademark of BD.

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Acronyms

AMTSL	Active management of third-stage labor
CHC	Commune health center
CI	Confidence interval
FIGO	International Federation of Gynecology and Obstetrics
ICM	International Confederation of Midwives
IU	International unit
MOH	Ministry of Health
MMR	Maternal mortality ratio
OR	Odds ratio
PPH	Postpartum hemorrhage
RR	Relative risk
VND	Viet Nam dong
WHO	World Health Organization

1. Executive Summary

Postpartum hemorrhage (PPH) is the major cause of maternal death globally and in Viet Nam. Active management of the third stage of labor (AMTSL) is now recommended internationally by the World Health Organization (WHO), International Federation of Gynecology and Obstetrics (FIGO), International Confederation of Midwives (ICM), and other agencies concerned with maternal health as a proven way to reduce PPH. Although AMTSL has been used on a pilot basis in some districts in Viet Nam, the Ministry of Health (MOH) has yet to adopt it as national policy because of concerns about implementation difficulties identified by some midwives related to use of ampoules and syringes and inadequate local data on effectiveness and cost implications.

The MOH and PATH agreed to collaborate on a study designed to evaluate the acceptability and ease of use of the Uniject prefilled, single-use injection device by midwives at primary and secondary level facilities, the effectiveness of AMTSL in reducing rates of PPH and the need for hemorrhage treatments, the cost-effectiveness of routine delivery of AMTSL, and the relative costs of using oxytocin in ampoules or in Uniject. The study was conducted in six districts of Thanh Hoa province from June to December 2004.

To evaluate user perceptions of acceptability among midwives already doing AMTSL, the study used baseline and post-intervention questionnaires with participating midwives in two districts where AMTSL is already routine practice and in a third district where AMTSL with Uniject was introduced as part of the effectiveness study.

The effectiveness of AMTSL versus no AMTSL was evaluated by comparing PPH rates and other outcomes in intervention and comparison districts. The primary outcomes regarding effectiveness of AMTSL with either standard syringes and with Uniject devices included PPH rates, duration of third stage, the need for additional treatment, and final maternal condition.

Relative costs or savings were evaluated by collecting actual and estimated direct costs in the project sites and then modeling them to estimate the cost or cost savings to the health system associated with routine use of AMTSL with oxytocin in Uniject compared to oxytocin in ampoules, and AMTSL compared to no AMTSL. The cost of oxytocin in Uniject was estimated at US$0.50 (VND 7,950). A simple sensitivity analysis was conducted, varying the cost of Uniject devices, the rate of PPH, and the treatment profile of severe PPH.

Among the 87 midwives who used Uniject devices, 98% answered that Uniject devices were easier to use than standard syringes (the remaining 2% said they were the same). Nearly 40% of midwives had reported in the baseline questionnaire that it was difficult to fill oxytocin into syringes, and about 30% more said it was time-consuming to fill oxytocin into syringes from ampoules. Midwives found the training materials to be useful and generally demonstrated good knowledge of AMTSL and Uniject.

A total of 3,607 eligible women were included in the effectiveness study (1,236 in the intervention district and 2,371 in the comparison districts). In the AMTSL district about half the oxytocin was administered by Uniject devices and the rest by standard syringes. The rate of hemorrhage 500 ml or greater was lower in the AMTSL district than in the comparison districts (3.4% versus 4.3%). However, several factors that could affect PPH (age, parity,

hospital delivery, and augmentation of stage one) were not similar in the intervention and comparison districts. After adjusting for these factors, PPH Ó500 ml was 34% less likely, prolonged third stage (greater than 30 minutes) was reduced by 80%, and extra oxytocin and bimanual compression were needed about 40% less often when AMTSL was used. Standard syringes and Uniject devices were equally effective in delivering oxytocin. There was no increase in retained placenta associated with cord traction.

AMTSL was inexpensive to provide and under certain conditions would be cost-saving. The savings associated with the reduced need for PPH treatment and reduced time waiting for delivery of the placenta (third stage) were subtracted from the unit cost of oxytocin to calculate a net incremental (additional) cost for providing AMTSL. This net incremental cost for routine provision of AMTSL at all deliveries by facility-based midwives to prevent PPH was only VND 3,896 (US$0.25) per woman using ampoules and VND 6,169 (US$0.34) using Uniject. If the current estimated unit cost of a Uniject device could be reduced by $0.10 to $0.40, Uniject would actually be slightly less expensive than ampoules. In other settings in Viet Nam or elsewhere, where the rate of PPH is only slightly higher than the 4.3% observed in our comparison districts, AMTSL becomes a cost-saving intervention. With a PPH rate of 5% and the same 40% reduction in treatment that occurred in our study, AMSTL using ampoules would save $900 per 100,000 deliveries. With a PPH rate of 8% both ampoules and Uniject devices are cost saving. With a PPH rate of 10%, AMTSL with ampoules would save $14,100 per 100,000 deliveries (about $190,000 each year for all the deliveries with skilled attendants in the whole country).

This is the first study to measure the effect of AMTSL in births in primary-level facilities in a low-resource country, and it supports several important conclusions:

- AMTSL leads to measurable reduction in the rate of PPH, even when underlying rates are already low, and reduces the need for extra treatment such as bimanual compression, with its attendant risk of infection.
- AMTSL substantially shortens the third stage of labor, enabling the midwife to attend to other needs of the mother and newborn more quickly.
- Controlled cord traction conducted as part of AMTSL is <u>not</u> associated with an increase in retained placenta.
- The reduced incidence of PPH not only benefits women's health but also reduces the demand on the health care system in terms of financial resources, staff time, supplies, and complex infrastructure.
- Midwives can easily learn AMTSL in a relatively short time, but putting it into practice using ampoules and standard syringes will be difficult sometimes in primary care facilities like commune health centers (CHCs), where midwives often practice without any assistance.
- Use of Uniject devices overcomes many of the barriers cited by midwives with regard to the use of oxytocin in ampoules and will be less expensive than ampoules if prices at the lower end of the likely range become available.

This study, added to the rest of the international evidence base, confirms the value of active management of the third stage of labor in lower rates of PPH, shortening the duration of the third stage, and reducing the need to provide additional treatment. To implement routine use of AMTSL, the MOH will need to include AMTSL in national policies and guidelines, train midwives and doctors, identify sources of oxytocin in ampoules with a full 10 IU dose, and consider adoption of oxytocin in Uniject devices when it becomes commercially available.

With these interventions, Viet Nam should be able to further reduce its maternal mortality, and hundreds of women's lives can be saved each year.

2. Introduction and Rationale

Postpartum hemorrhage (PPH) is the major cause of maternal death globally and in Viet Nam. Based on the recent Maternal Mortality study in 2001 conducted in seven provinces by the Ministry of Health (MOH) with support from the World Health Organization (WHO) and Population Council, the MOH has estimated the average national maternal mortality ratio (MMR) to be about 165 per 100,000 live births.[1] Data from the seven-province study suggest that 41% of all direct maternal deaths (or 31.3% of all maternal deaths, direct and indirect) are due to hemorrhage[2]; an earlier study in Vinh Phu showed 53.1% of all direct causes of maternal mortality were due to hemorrhage.[3] To achieve the Millennium Development Goal of reducing maternal mortality by 75% by 2015, the rate of deaths due to postpartum bleeding must be dramatically reduced.

Active management of the third stage of labor (AMTSL) is a process that initially involved oxytocin (10 International Units, or IU) used in combination with controlled cord traction and prompt clamping of the umbilical cord. Based on several studies, including a Cochrane systematic review, AMTSL is now recommended internationally by WHO and other agencies concerned with maternal health.[4] In 2003 the International Confederation of Midwives (ICM) and International Federation of Gynecology and Obstetrics (FIGO) issued a joint statement calling for global adoption of AMTSL, in which they included use of uterotonic drugs (like oxytocin), controlled cord traction, and uterine massage after delivery of the placenta (rather than prompt cord clamping).[5]

Although AMTSL at commune health center (CHC) level is not part of the official national guidelines, the MOH has agreed to its pilot use in a few districts and listed it as a strategic solution to be considered in the Safe Motherhood Master Plan for 2003–2010.[6] In the pilot projects, some midwives at CHCs have reported difficulties doing AMTSL in the midst of other delivery activities without an assistant to help them to break the ampoules and prepare a standard injection, a particular problem for night or home deliveries when an assistant is not usually available. Since more than 75% of all births in Viet Nam occur at commune level, of which 80% of deliveries are with skilled midwives either at home or in CHCs, making AMTSL easier for these midwives would be likely to increase the adoption of this practice. In addition, there are concerns about risky recapping of needles, inappropriate breaking of glass ampoules, and waste disposal with sharps around health facilities. The Uniject⊗ prefilled, single-use injection device (BD Pharmaceutical Systems, New Jersey USA) offers a potential answer to these concerns about ampoules and standard syringes.

The purpose of this study is to provide a local evidence base on AMTSL and oxytocin in Uniject to assist the MOH in formulation of national policy regarding postpartum care. The MOH and PATH agreed to collaborate on a study designed to evaluate the acceptability and ease of use of the Uniject device by midwives at primary and secondary level facilities, the effectiveness of AMTSL in reducing rates of PPH and the need for hemorrhage treatments, the cost-effectiveness of AMTSL, and the relative costs of oxytocin in ampoules and in Uniject devices.

3. Literature Review

3.1 Uterine atony as the primary cause of PPH

Obstetric hemorrhage is a major cause of maternal mortality and morbidity worldwide, with an estimated 14 million cases occurring each year.[7] While rates between and within countries vary greatly, hemorrhage accounts for roughly 25% of maternal deaths globally.[8] PPH is the most common type of obstetric hemorrhage, and in some settings, the most common cause of maternal death. It is usually defined as excessive vaginal bleeding (blood loss greater than 500 ml) within 24 hours, but this definition is problematic, and studies indicate that estimated blood loss is commonly about half the actual loss.[9] In Viet Nam a cutoff of 300 ml has been used, partly reflecting concern about widespread underestimation and also in light of the smaller size of Viet Namese women and relatively high rates of anemia among pregnant women (32%).[10] Immediate PPH, heavy bleeding directly following childbirth or within the first 24 hours thereafter, is the most common type of PPH and can be caused by uterine atony, retained placenta, inverted or ruptured uterus, and cervical, vaginal, or perineal lacerations.

Uterine atony, when the uterus fails to contract properly after delivery, is the most important cause of immediate PPH.[11] The main risk factors for PPH due to uterine atony in the developing world include pre-eclampsia, prolonged labor, and high parity. Atony is also more likely to occur in women whose labor is initiated or augmented with oxytocin, who receive high concentrations of halogenated anesthetic agents that relax the uterus, who are grand multiparous or have previously had PPH, or who have large or multiple fetuses. [12] However, roughly two-thirds of women who suffer from PPH present no risk factors.

3.2 Oxytocin and active management of third stage of labor for prevention

Drugs that cause contraction of the uterus (uterotonics) play a critical role both in prevention and treatment of PPH. Oxytocics (oxytocin, ergometrine, and combinations of the two) and prostaglandins (e.g., misoprostol, carboprost) have various advantages and disadvantages, and there is not yet an ideal agent for all low-resource settings. Although oxytocin requires injection, it is more effective and less expensive than prostaglandins. Uterotonic drugs, used alone or in combination with cord traction and uterine massage (AMTSL), are the primary interventions known to reduce the incidence of PPH. Another preventive measure is to reduce the incidence of prolonged labor (through the use of the partograph and timely intervention, when needed).

Studies in other countries. A Cochrane systematic review of seven trials involving over 3,000 women concluded that prophylactic oxytocin reduced the risk of PPH (> 500 ml) by 50% and the need for therapeutic oxytocics by 50% compared to no uterotonics.[13] The same review found that ergot alkaloids had similar efficacy, but oxytocin was associated with fewer manual removals of the placenta and less frequent raised blood pressure. In the Prendiville et al review,[4] five studies of AMTSL were reviewed, and it was concluded that AMTSL significantly reduced mean maternal blood loss, PPH greater than 500 ml, and the duration of the third stage of labor. A recent WHO multicenter trial comparing oxytocin and misoprostol has concluded that oxytocin is the most effective uterotonic medication for preventing PPH.[14] An earlier WHO study of the stability of oxytocic drugs concluded that parenteral oxytocin is more stable than parenteral or oral ergometrine or methylergometrine and should therefore be preferred over them, given their similar efficacy, greater stability, and reduced side effects.[15]

Studies in Viet Nam. A study of the effect of AMTSL involving over 1100 women in Hanoi Obstetric and Gynecological Hospital in 1996 concluded that AMTSL reduced the time of delivery of the placenta by 50% ($p < 0.001$) and significantly reduced mean maternal blood loss ($p < 0.001$) compared to routine methods (no uterotonics, cord traction, uterine massage, or immediate clamping).[16] A similar study conducted in Quang Xuong district hospital with 567 women found that the efficacy was similar, with a PPH rate that was 40% lower in the intervention group compared with a comparison group ($p < 0.05$).[17]

Two studies evaluating umbilical vein administration of oxytocin in the third stage of labor in the National Obstetric and Gynecological Hospital concluded that administration of oxytocin significantly reduced blood loss and the duration of the third stage of labor, and that this method is simple and inexpensive and should therefore be recommended for application.[18,19]

A recent national obstetric and gynecological hospital study evaluating rectal misoprostol for prevention of hemorrhage during the third stage of labor concluded that rectal misoprostol significantly reduced mean maternal blood loss, PPH greater than 500 ml, and the mean duration of the third stage of labor.[20] Another study of Tu Du Obstetric and Gynecological Hospital using a placebo-controlled trial found similar efficacy for misoprostol in reducing blood loss and duration of the third stage of labor.[21]

3.3 Use of Uniject devices for oxytocin and other medicaments

A significant challenge with all the oxytocics (as opposed to some prostaglandins) is that they require injection, either intramuscularly or intravenously. Ensuring safe injection practices—sterile syringes and needles, accurate dosing, and safe disposal—is difficult in many settings, but particularly in home deliveries and small community maternity facilities or health centers. The Uniject prefilled injection device offers a solution to some of these problems, since it guarantees a sterile, non-reusable device with an accurate dose. Midwives participating in a study using oxytocin in Uniject devices in home deliveries in Indonesia substantially improved their injection practices and found the Uniject much easier to use than ampoules and standard syringes.[22] In a hospital-based study in Luanda, Angola, AMTSL was introduced using oxytocin in Uniject; PPH Ó 500 ml was reduced by more than half as a result, and the duration of the third stage was also greatly reduced.[23]

Uniject devices have been used with a variety of other medicaments, including injectable contraceptives in Brazil,[24] tetanus toxoid in Bolivia,[25] and hepatitis B vaccine in Indonesia,[26] and has been registered for commercial use by companies in Indonesia and India. All five million of Indonesia's newborns will receive hepatitis B vaccine at birth with Uniject devices. The Uniject device is being used to deliver nine million doses of tetanus toxoid to women in remote populations in Mali, Afghanistan, Ghana, Somalia, Sudan, and Burkina Faso.[27]

4. Study Methods

Full details of study methods are provided in Appendix A.

4.1 Study design

The study was designed with three main components to address key questions about acceptability and ease of use of Uniject, the effectiveness of AMTSL in reducing hemorrhage and its consequences, and the cost or cost savings involved in using AMTSL and oxytocin in

Uniject. In a small fourth component, information was collected on the physical performance of the Uniject devices and any logistics barriers encountered.

To evaluate user perceptions of acceptability among midwives already doing AMTSL, the study used baseline and post-intervention questionnaires with participating midwives in two districts where AMTSL is already routine practice and in a third district where AMTSL with Uniject was introduced as part of the effectiveness study.

The effectiveness of AMTSL versus no AMTSL was evaluated by comparing PPH rates and other outcomes in intervention and comparison districts. The primary outcomes regarding effectiveness of AMTSL with either standard syringes and with Uniject devices included PPH rates, duration of third stage, the need for additional treatment, and final maternal condition. Bleeding was considered as normal if it was measured at < 300 ml; blood loss of 300–499 ml met the Viet Namese definition of PPH and was considered "high normal" for this study. Blood loss of 500–999 ml was considered moderate PPH, and loss of 1,000 ml or more was considered severe PPH.

Relative costs or savings were evaluated by collecting actual and estimated direct costs in the project sites and then modeling them to estimate the cost or cost savings to the health system associated with routine use of AMTSL with oxytocin in Uniject compared to oxytocin in ampoules, and AMTSL compared to no AMTSL. The study was limited to costs from a health service perspective and did not include patient out-of-pocket costs or social costs (patient or family member time). The primary outcomes included: the direct cost of normal delivery without AMTSL, normal delivery at CHC with AMTSL (with ampoule and with Uniject), treatment of PPH at CHC and cost of referral to district hospital, and treatment of PPH at district and provincial hospitals.

Assessment of logistic and device performance was based on prospective collection of data by midwives using Uniject devices and informal interviews with midwives, their supervisors, and managers of drug stores and distribution.

4.2 Location and participants

The study was conducted in six lowland districts in Thanh Hoa province in the North Central Region of Viet Nam, where safe motherhood activities had already been initiated and where provincial and certain district hospital staff had already been trained in AMTSL. All study districts were in the eastern part of the province close to the provincial city.

The acceptability study was carried out in Quang Xuong and Nong Cong districts, where health workers had already received training on AMTSL, and in Hoang Hoa district, which introduced AMTSL during the study. The effectiveness study was carried out in one intervention district (Hoang Hoa) and three comparison districts (Tinh Gia, Trieu Son, and Thieu Hoa). All district hospital and CHC midwives in the intervention and comparison districts were included in the effectiveness study, and all consecutive women (18 years and older, whether at home or in a facility) completing second stage of labor vaginally (and therefore suitable for AMTSL) while under the care of participating midwives during the study period were eligible for enrollment. Cost data were gathered from a sample of two CHCs and the district hospital in each of four districts (two from the acceptability study and two from the effectiveness study districts) in December 2004, as well as in the Thanh Hoa

Obstetric and Gynecology Hospital. Logistics data were gathered in all districts where Uniject devices were used.

4.3 Measurement of blood loss and definition of AMTSL

After delivery of the newborn, a plastic drape was placed under the woman's hips so that blood could be channeled into a tray placed at the foot of the delivery table. After completion of the delivery, the tray was emptied into a smaller plastic cylindrical basin which had markings drawn on at 300 ml, 500 ml, and 1,000 ml. In most home deliveries, midwives also used the plastic drape, placed the tray under the bed, and then used the basin to measure the blood.

The study sites followed a modified version of the protocol for AMTSL previously used in the Quang Xuong NGO Networks for Health Safe Motherhood project training protocol. The final protocol, approved by the MOH and used in the training, included:

- Routine intramuscular injection of 10 IU of oxytocin within two minutes after the birth.
- When the uterus is contracted, exertion of controlled cord traction with one hand while the other hand is placed above the pubis to guard the uterus.
- Uterine massage to stimulate contractions.

Although it was not part of the official protocol, immediate cord clamping was also taught during the training.

4.4 Training

The training team consisted of experienced obstetricians and midwives from national and provincial levels of the MOH and resource staff from PATH. For the acceptability study, midwives in Quang Xuong district attended a half-day training. Midwives in Nong Cong went through the full training for the effectiveness study (described below) before they were switched to this component of the study. For the effectiveness study, 54 midwives in the intervention district attended four days of training, which included 1.5 days of classroom work and 2.5 days at the district and provincial hospitals for clinical practice. Midwives (142) in the comparison districts of the effectiveness study attended two days of training, one for classroom work and one for clinical practice. Information on the topics included in training is given in Appendix A.

4.5 Materials

Uniject is a non-reusable device consisting of a plastic blister with a drug reservoir and a neck to which a needle is permanently attached by means of a hub (Figure 1). For this study, Uniject was filled with sufficient oxytocin to ensure a dose of 10 IU. The oxytocin-filled Uniject devices were kept outside the cold chain at CHC level and returned to the district hospital for refrigerated storage and use if not used within two months. Those used at the district hospital were kept refrigerated until they were used. Full details on this and other materials are in Appendix A.

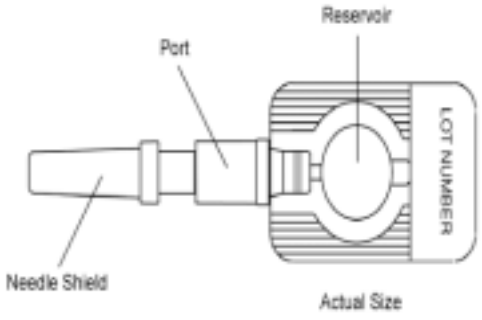

Figure 1. Uniject Injection Device

4.6 Data collection and analysis

Details of data collection and analysis methods are provided in Appendix A.

4.7 Ethical review

The study protocol was approved by the Scientific Committee of the MOH in Viet Nam, the Columbia University Institutional Review Board, and PATH's Human Subjects Protection Committee. Details on informed consent are given in Appendix A.

5. Results

Key findings on acceptability, effectiveness, and costs are presented below, but details of all results are available in Appendix B.

5.1 Acceptability and ease of use

A total of 216 midwives in six districts participated in the study, of whom 87 in three districts completed post-intervention questionnaires about their experience with AMTSL and Uniject devices. In the baseline questionnaire, when midwives were asked what difficulties they frequently had when preparing or injecting oxytocin with standard syringes, the most common response was that it was difficult to fill oxytocin into the syringe, with the next most common complaint being that it was time-consuming to fill oxytocin into the syringe (Table 1). One midwife at CHC level said: *"I have difficulties administering oxytocin within two minutes after the baby is born because it takes time to open the package of the syringes and fill the oxytocin in them. This is a particular problem for fast deliveries, when it may make the oxytocin be given too late."*

Table 1. Difficulties with standard syringes, on baseline survey (n=52)

Comment	No.	(%)
Difficult to fill oxytocin into syringes	20	(38.5)
Time-consuming to fill oxytocin into syringes	15	(28.8)
Not sure of dose accuracy	4	(7.7)
Not sure oxytocin given in time	4	(7.7)
Not convenient	1	(1.9)
No difficulty	7	(13.5)

During the two-month intervention period, midwives in Quang Xuong and Nong Cong used about 400 Uniject devices while midwives in Hoang Hoa used about 650. On average each midwife used about 11–12 devices. Based on this experience, 98% answered that Uniject devices were easier to use than standard syringes (the remaining 2% said they were the same). The main reason given was convenience (Table 2). One midwife commented: "*It is easier to use because one dose is ready prepared in Uniject and we only have to take out the packing, activate it, and inject into the muscle of the leg.*"

Table 2. Reasons Uniject devices were easier to use than standard syringes

Reasons given	QX, NC districts No.	(%)*	HH district No.	(%)*
Convenience	28	(77.8)	33	(64.7)
Easy to use	16	(44.4)	13	(25.5)
Faster than ampoule	9	(25.0)	4	(7.8)
Simple	3	(8.3)		
Safe	1	(2.8)		

*More than one answer could be given, so total is >100%.

Similarly, all 87 midwives said they preferred using Uniject devices over ampoules and standard syringes. Again, convenience was the predominant reason mentioned by more than 70% of all midwives, ease of use was mentioned by more than half, and being faster was mentioned by nearly 20% of the midwives in Hoang Hoa. Almost all (97.6%) rated it easy to activate and inject with Uniject devices. One said that she found it difficult to activate at first, but she later had no problem with it.

When asked what single thing they liked most about Uniject devices, convenience and ease of use were at the top of the list. As one midwife said: "*(It) is easy to use because we don't need to break the glass ampoules and fill the drug into the syringe, especially when there is only one person on duty.*" When asked what single thing they liked least about Uniject compared to standard syringes, half said there was nothing, nine midwives (10%) cited the need to activate the device before use, two mentioned that it could not be reused, one mentioned difficulty squeezing the reservoir, and 30 (34%) were concerned because they believed the oxytocin in Uniject had to be kept in a refrigerator and returned every month to the district (a special study procedure). All midwives said they wanted to use Uniject devices in the future, except for one who did not because she thought it needed to be exchanged every month if it was not kept cold.

Written instructions. Midwives uniformly said that the written instructions about Uniject were easy to understand. Seven (8%) mentioned the pictures as helpful, while others noted that it was easy to follow (12), short (6), specific and detailed (4), clear (4), and in suitable local language (3). Most had no comments about how to improve it, but two suggested it could be shorter and one wanted more practice during training.

Effectiveness of training materials. When assessed for their knowledge about Uniject devices and use of oxytocin several months after training, most midwives were well informed, but there were a few points where clarification and refresher training are needed. In Quang Xuong and Nong Cong only one midwife missed any of the questions about Uniject features. In Hoang Hoa five midwives did not check the item about Uniject being single-use, but only one specifically said that Uniject could be reused; 35% responded that the volume was more than one dose (probably because of confusion about the concept of over-filling to ensure expulsion of a correct dose). All but one midwife knew that activation should be done before removing the needle cap, and all knew how to tell if activation had occurred. There was confusion about aspiration (which is not necessary with oxytocin since it can also be safely administered intravenously), with the vast majority suggesting that aspiration be done by pressing the reservoir after injecting the needle. Aspiration was not specifically mentioned during the training. While most midwives knew not to recap the needle, 14% replied that the

device should be recapped before disposal. Only 60% of midwives correctly understood that oxytocin can safely be stored at room temperature for at least 2 to 3 months; 31% thought it must always be refrigerated, while 9% thought it needed no refrigeration at all.

Conducting AMTSL. In the baseline survey in Quang Xuong and Nong Cong, midwives correctly identified key elements of AMTSL such as giving oxytocin (98%), controlled cord traction (85%), counter-pressure upward on the uterus (81%), and clamping the cord promptly (50%). One-third incorrectly mentioned checking the birth canal for lacerations as part of AMTSL. All routinely administered oxytocin: 15% when the anterior shoulder was born, 60% within two minutes after the baby was born, 8% more than two minutes after the baby's birth but before the placenta was delivered, and 17% at other times. Midwives in Hoang Hoa were asked to comment on the difficulty of conducting AMTSL (since it was new for them). Two-thirds said that administering oxytocin with ampoules and standard syringes was "somewhat difficult," while only two midwives (4%) rated oxytocin with Uniject as somewhat difficult to administer. Everyone else rated it as easy. One-quarter rated controlled cord traction as somewhat difficult, while the rest considered it easy.

5.2 Effectiveness

Effectiveness results come from the four districts (one intervention and three comparison) that tracked all eligible births during the study period. A total of 3,607 eligible women were included in the effectiveness study (1,236 in the AMTSL intervention district and 2,371 in the comparison districts). Women in the AMTSL and comparison districts differed somewhat on key characteristics of age, parity, place of delivery, and stage one augmentation (Table 3). Since these factors were also associated with risk of PPH, they were subsequently included in the multivariate logistic regression analysis. More than 95% of women in the AMTSL district received 10 IU of preventive oxytocin, uterine massage, and controlled cord traction; a few did not receive any oxytocin and about 2% received only one ampoule of 5 IU. About half the oxytocin was administered by Uniject devices and the rest by standard syringes.

Table 3. Characteristics of participating women

	AMTSL		Comparison	
	No.	**%**	**No.**	**%**
Total	1,236	100.0	2,371	100.0
Age				
18-19 yr	40	3.2	143	6.0
20-34 yr	1,115	90.2	2,057	86.8
Ó35 yr	81	6.6	171	7.2
Parity*				
1	590	47.9	1,245	52.8
2-3	585	47.5	1,040	44.1
4-7	57	4.6	73	3.1
Place of delivery				
CHC	1,087	87.9	1,750	73.8
Home	15	1.2	26	1.1
Hospital	134	10.8	595	25.1
Oxytocin in Stage 1	29	2.3	80	3.4

* Including current delivery; missing data on 4 in AMTSL and 13 in Comparison

Bleeding outcomes. Hemorrhage according to the Viet Namese definition of bleeding of 300 ml or more was relatively common in both groups (about 19%). However, using the international definition of 500 ml or more, PPH was less common in the AMTSL district than in the comparison districts (3.4% versus 4.3%). Severe PPH was rare (Table 4). PPH specifically due to atony was also lower in the AMTSL district (2.3% versus 3.0%). The rates of retained placenta were very similar in the two groups, with no apparent effect due to the use of controlled cord traction. The effect of AMTSL in shortening the third stage of labor was dramatic, reducing the number with a third stage greater than 15 minutes by 88% and those with a third stage greater than 30 minutes by 77%. Atony was the primary cause of PPH in both groups.

Table 4. Bleeding outcomes

	AMTSL		Comparison	
	No.	**%**	**No.**	**%**
Total	1,236	100.0	2,371	100.0
Postpartum Bleeding				
Normal	1,001	81.0	1,921	81.0
High normal	193	15.6	347	14.6
Moderate PPH	33	2.7	91	3.8
Severe PPH	9	0.7	12	0.5
Cause-specific PPH				
Atony	29	2.3	71	3.0
Retained placenta	6	0.5	10	0.4
Tears	6	0.5	21	0.9
3rd stage duration*				
> 30 minutes	13	1.1	108	4.6
> 15 minutes	67	5.4	1,098	46.7
Source of PPH (Ó500)		**% of PPH**		**% of PPH**
Atony	29	69.0	71	69.0
Retained placenta	6	14.3	10	11.0
Tears	6	14.3	21	18.6
Other	1	2.4	1	1.4

*Missing data on 1 in AMTSL group and 21 in comparison group

Treatment outcomes. Regardless of the level of bleeding recorded by the midwives, they responded with treatment activities based on their clinical perceptions of the need. With regard to atonic uterus, they administered extra doses of oxytocin (usually with uterine massage) and performed bimanual compression of the uterus (see Table 5). AMTSL resulted in a 40% lower use of these treatment interventions.

Table 5. Treatments given for bleeding due to atonic uterus

	AMTSL		Comparison		Relative Risk
	No.	%	No.	%	(95% CI)
Total	1,236	100.0	2371	100.0	
Any oxytocin given for PPH Ó500 ml	52	4.2	164	6.9	0.61 (0.45, 0.82)
Bimanual compression	28	2.3	97	4.1	0.55 (0.36, 0.84)
Either oxytocin or bimanual compression	61	5.0	184	7.9	0.64 (0.48, 0.85)

In this study, women were referred for higher level care only rarely. Altogether only 12 women (0.3%) were referred to a higher level facility, and none of these was for PPH due to atony. Although the number of women needing special care beyond additional oxytocin and bimanual compression was small, these women did require additional resources from the health care system. Of those with PPH due to atony, 31 delivered in a district hospital. Most (87%) were given intravenous fluids, seven women received a transfusion (average of 1.6 units of blood in the AMTSL district and 2.5 units in the comparison districts), and one in a comparison district had a hysterectomy. Women with atony in the AMTSL district stayed in the hospital somewhat longer than those in the comparison districts (average of 5.3 days versus 3.8 days). The level of treatment needed once PPH occurred did not differ substantially between the AMTSL and comparison groups in this small group of patients.

There was no difference in the final outcome among women once they had a PPH due to atony, with 93.1% of the AMTSL group and 94.4% of the comparison group being discharged home in good condition. During the study period there was one maternal death (MMR of 27/100,000 births).

Unanticipated district differences. In addition to the differences in age, parity, place of delivery, and need for oxytocin augmentation in stage one labor between the AMTSL and comparison group districts as a whole (see above in Table 3), there were sharp differences among the three districts within the comparison group with regard to certain outcomes and use of oxytocin in the first stage of labor. Thieu Hoa reported much lower rates of PPH for both atony and retained placenta (but not for tears), but their use of treatments like additional oxytocin and bimanual compression were similar to (or higher than) the other districts. Historically, Thieu Hoa has also reported lower rates of PPH than any of the other districts. Because of these differences (more details in Appendix B), the analysis was done both including and excluding Thieu Hoa.

Multivariate analysis of effectiveness of AMTSL. Multivariate logistic regression analysis makes it possible to adjust for the effects of extraneous factors while identifying the specific risk associated with the intervention. The odds ratio (OR) estimates how likely an outcome like PPH was in the AMTSL intervention district as compared to the non-AMTSL districts. An OR above 1.0 means the intervention increases the likelihood or risk, while an OR below 1.0 shows a reduction in risk compared to the reference group. The logistic model adjusted for age (Ó35 years), parity (Ó3 prior births), place (hospital vs. CHC/home), and first-stage augmentation. Three versions of the models were run: (1) all cases, (2) excluding Thieu Hoa

because its PPH rate was inconsistent with the amount of treatment provided, (3) excluding those with first-stage augmentation.

With all cases included, AMTSL is associated with a 19% non-significant reduction in PPH Ó 500 ml generally and a slightly lesser reduction of PPH specifically due to atony (Table 6). However, there is a significant reduction in PPH of about 35% and of PPH due to atony of about 30%, when either Thieu Hoa is excluded or stage-one augmentation cases are excluded. The 80% reduction in prolonged third stage beyond 30 minutes was dramatic in all three versions of the model. The reduction in third stage duration beyond 15 minutes was even more remarkable, with at least a 90% drop in risk. The need for extra treatment—either additional oxytocin or bimanual compression—was significantly reduced, by 30-40%, in nearly all models.

Table 6. Logistic regression analysis of key outcomes

Outcomes	Adjusted Odds Ratio*	95% CI
Model 1 – all cases (n = 3,607)		
PPH Ó500 ml [a]	0.81	0.56, 1.2
PPH due to atony [a]	0.84	0.54, 1.3
3rd stage > 30 minutes [b]	0.20	0.11, 0.35
3rd stage > 15 minutes [b]	0.06	0.04, 0.07
Any oxytocin given [a]	0.68	0.49, 0.94
Bimanual compression given [c]	0.63	0.41, 0.98
Model 2 – without Thieu Hoa (n = 2,738)		
PPH Ó500 ml [d]	0.66	0.45, 0.98
PPH due to atony [d]	0.69	0.43, 1.1
3rd stage > 30 minutes [e]	0.21	0.11, 0.38
3rd stage > 15 minutes [e]	0.07	0.05, 0.09
Any oxytocin given [d]	0.66	0.46, 0.93
Bimanual compression given [f]	0.68	0.43, 1.1
Model 3 – without stage 1 augmented cases (n = 3498)		
PPH Ó500 ml [g]	0.66	0.44, 0.99
PPH due to atony [g]	0.70	0.43, 1.1
3rd stage > 30 minutes [h]	0.20	0.11, 0.36
3rd stage >15 minutes [h]	0.06	0.04, 0.08
Any oxytocin given [g]	0.60	0.42, 0.85
Bimanual compression given [i]	0.61	0.39, 0.96

*Reference = comparison districts; adjusted for age Ó35, parity Ó4, hospital delivery, and (in Models 1 and 2) stage 1 augmentation with oxytocin

a – 17 missing; b – 39 missing; c – 104 missing; d – 12 missing; e – 26 missing; f – 81 missing; g – 16 missing; h – 22 missing; i – 82 missing

Comparison of standard ampoule and syringe versus Uniject device. Since midwives in Hoang Hoa performed AMTSL using both standard syringes and Uniject devices during the study, it was possible to make a direct comparison. AMTSL was equally effective with either device, confirming that Uniject provides a comparable dose of oxytocin.

5.3 Cost

Average unit costs were calculated both for normal deliveries and for treatment of PPH, based on the health service perspective and including only direct costs. Out-of-pocket costs by patients and time and opportunity costs for patients and their families were not included, except the cost of transport for referral (which is sometimes paid by the system and sometimes by the patient). The cost of oxytocin in ampoules was VND 6,000 for two 5 IU ampoules, and VND 500 for a disposable syringe and needle. The oxytocin in Uniject devices was donated for the study. Since it is not yet commercially available, its unit cost was estimated at US$0.50 (VND 7,950). Details on how costs were calculated are in Appendix C.

Base model of delivery and PPH treatment costs. The basic costs for normal deliveries with and without AMTSL and for treatment of PPH at different facility types are listed in Table 7. Treatment costs are added to whatever the normal delivery cost. The net incremental cost takes into account the cost of adding oxytocin while also considering the savings that result from reduced PPH treatment costs or shorter third stage. The additional net cost per woman of providing AMTSL with ampoules and syringes was just VND 3,896 (US$0.25), and using Uniject devices would only cost VND 1,557 (US$0.10) per woman more in these particular districts. In many cases, women will pay for this cost themselves, especially if they understand the value of AMTSL.

Table 7. Base model of delivery and PPH treatment costs (per woman)

	VN Dong	US$*
Cost of normal delivery		
At CHC, without AMTSL	21,297	1.34
At CHC, with AMTSL, ampoule	26,442	1.66
At CHC, with AMTSL, Uniject	27,840	1.75
At district hospital, without AMTSL	21,194	1.33
At district hospital, with AMTSL, ampoule	30,341	1.91
At district hospital, with AMTSL, Uniject	31,444	1.98
Cost of treating PPH		
At CHC, moderate, without referral	56,552	3.56
At CHC, severe, with referral	140,679	8.85
At district hospital, if delivered there, moderate	166,509	10.47
At district hospital, if delivered there, severe	582,019	36.60
At district hospital, if delivered there, severe+	1,018,648	64.07
At district hospital, if referred in, moderate	185,531	11.67
At district hospital, if referred in, severe	580,041	36.48
At district hospital, if referred in, severe+	1,027,170	64.60
At provincial hospital, if referred in, severe+	1,112,105	69.94
Net incremental cost per woman receiving AMTSL		
Net incremental cost of adding AMTSL, ampoule	3,896	0.245
Net incremental cost of adding AMTSL, Uniject	5,453	0.343

* Assumes US$1 = VND 15,900

With approximately 130 maternal deaths per 100,000 live births in Viet Nam,[28] of which perhaps 30% are due to PPH, AMTSL might be expected to prevent 40% of those PPH deaths, or 15.6 deaths per 100,000 live births. If each woman received AMTSL, it would cost an additional US$24,500 for 100,000 deliveries (with ampoules) and cost just over US$1,570

per life saved. At a maternal mortality ratio of 165,[29] the number of deaths prevented would be about 19.8/100,000, and the cost per death prevented would drop to about US$1,240.

Sensitivity analyses using different assumptions. Costs were recalculated using different costs for Uniject, different PPH rates, and a higher estimate for treating severe cases (Table 8). The Uniject device cost was modeled at a low cost of $0.40 and a high of $0.75. At the lower cost, Uniject would actually be slightly less expensive than ampoules (VND 34; $0.002); at the higher cost, use of Uniject devices would be $0.35 higher per woman than ampoules. Varying the rate of PPH had the biggest effect, as might be expected. In other settings in Viet Nam or elsewhere, where the rate of PPH is only slightly higher than the 4.3% observed in our comparison districts, AMTSL becomes a cost-saving intervention. Even just increasing the PPH rate to 5% (without AMTSL) and assuming the 40% reduction in treatment that occurred in the study (adjusted for other factors), AMTSL becomes modestly cost saving with ampoules ($900 per 100,000 women). With a PPH rate of 8%, AMTSL with either device is cost saving, and at a PPH rate of 10%, AMTSL with ampoules would save $14,100 per 100,000 women (about $190,000 each year for all the deliveries with skilled attendants in the whole country). Changing the assumption about the proportion of severe PPH cases needing surgical treatment reduced the net incremental cost only slightly (by 6%) over that of the base case, but this effect would be bigger under the higher PPH rate assumptions.

Table 8. Net incremental cost (or savings) of AMTSL with varied assumptions

	Ampoule		Uniject	
	VND	US$	VND	US$
Base case	3,896	0.245	5,453	0.343
Uniject price (base = $0.50)				
$0.40	3,896	0.245	3,862	0.243
$0.75	3,896	0.245	9,432	0.593
PPH rates (base = 4.3%)				
5%	(144)	(0.009)	1,232	0.077
8%	(1,402)	(0.088)	(23)	(0.001)
10%	(2,234)	(0.141)	(854)	(0.054)
Very severe (base = 10%)				
25% of severe	3,656	0.230	5,489	0.345

5.4 Logistics: device performance, storage, and disposal

There were very few problems with Uniject device performance or handling. Three midwives (out of 87 who completed a final survey after using Uniject) reported one leaking Uniject device, two with cracks, and one with a dent, for a total of four problems out of 1,050 devices used (0.4%). No problems were reported with cold storage at provincial or district level. Procedures for releasing devices to CHCs and to hospital midwives were a bit cumbersome, but that was in the context of a study where careful tracking was required. Monthly resupply to CHCs could be easily accomplished when midwives or heads of CHCs attend monthly meetings at district level.

When ampoules and syringes were used, a variety of steps were involved in disposal. More than 80% of midwives specifically mentioned disposing of standard syringes in a safe box or

a bottle after use; 13% mentioned disinfection with 0.5% chlorine as well. About half reported that sharps were burned before burial, while the remainder were just buried in a designated area. Ampoules were sometimes put in with other sharps and sometimes just collected and buried. All midwives who used Uniject devices reported that they were put into safety boxes or bottles. Although only 55% specifically mentioned burning and burying them afterwards, it is assumed that the disposal pattern was similar to that with other sharps.

6. Discussion

6.1 Acceptability and correct use

The perceptions reported by midwives in this study were similar in many ways to those reported by midwives in Indonesia and elsewhere regarding the substantial improvement the Uniject device represented in terms of ease of use and convenience. Unlike the case in Indonesia where syringe reuse without proper sterilization was a common occurrence, disposable syringes seem to be readily available in the study districts. Safe injection was not a major problem, at least in these relatively well-resourced districts. To the extent that sterile syringes were not always available at the time of delivery, having oxytocin available in Uniject devices would provide a guarantee of safety. In a setting where oxytocin is usually provided in 5 IU ampoules, there is also a risk of under-dosing as midwives may give only one ampoule. Midwives at CHCs also reported instances where they were unable to administer oxytocin within the recommended timeframe (within two minutes after birth) because of the other demands on their time at this crucial moment and the complications of breaking two ampoules, opening and filling a syringe. Speed was mentioned by at least 15% of midwives as a particular advantage of Uniject.

It is not surprising that a midwife would find breaking ampoules to be cumbersome at the time of delivery, especially when she is the lone attendant. The possibility of injury is always there. In addition, studies have talked about the risk of glass splinters from ampoules getting injected inadvertently and have called for manufacturers to switch to plastic ampoules as soon as possible.[30,31]

Training midwives to do AMTSL and to use Uniject devices was relatively brief and very effective. There were few problems with activation or use. Two points will need greater emphasis in future training: that aspiration is not necessary with oxytocin, and that clearer explanations about proper cold storage (depending on actual product requirements) should be given so that full advantage can be taken of oxytocin's heat stability while prolonging its life by using cold storage where available.

6.2 Effectiveness of AMTSL

The study demonstrated that AMTSL can successfully reduce the rate of PPH, shorten the duration of the third stage, and reduce the need for extra treatment. The effect on the length of the third stage is consistent with other studies. It appears that the effect of AMTSL in reducing the rate of PPH was not quite as great in this study as has been reported in other studies, but the underlying rate of PPH in this population was already relatively low (4.2%). For example, in the Hinchingbrooke study in UK the rate of PPH in the expectant management group was 16.5%,[32] and a study in Ghana reported a PPH rate of 17.4% in the group with active management.[33] The results here reconfirm other studies in Vietnam showing a positive benefit from AMTSL using rectal misoprostol and umbilical vein administration of oxytocin. The low rate of PPH here may be a reflection of the high quality

of midwife attendance (about half have at least ten years of experience), the relatively low parity, and the low level of medical intervention in the delivery process. The refresher training in the use of the partograph may have also contributed to the low rates. The maternal mortality ratio during the study period was extremely low. In other provinces where such favorable conditions are not present and PPH rates are higher, the expected benefit should be higher.

The reduction in extra treatment was consistent and statistically significant across all three models, even though Model 1 suggests a smaller and non-significant reduction in PPH. It is not clear why Thieu Hoa district reported such a low rate of PPH compared to its reported use of treatment. That atypical performance clearly made the effect of AMTSL appear less beneficial, as is apparent in Model 2 when Thieu Hoa was removed from the comparison group. Since their rate of treatment associated with PPH (oxytocin and bimanual compression) was actually similar to the other districts, it is possible that other factors of clinical condition (beyond blood loss) that were not captured in this study influenced midwives in Thieu Hoa to provide treatment.

It is reassuring to see that there was no increased risk of retained placenta associated with AMTSL. While there have been concerns raised about cord traction, other studies have also generally shown no significant effect on retained placenta.[34,35]

The role of augmented stage one labor as a risk factor for PPH is presumed to be due to over-stimulation and fatigue of the uterine muscle. The uneven distribution of such cases and their severity among the four districts was managed in Models 1 and 2 by including it as a confounding factor and in Model 3 by excluding the 109 women who received oxytocin in stage one of labor.

6.3 Costs

The actual cost of routine use of AMTSL per woman is very small and would actually be cost saving in districts with more typical rates of PPH than those found in this study. In addition to all the illness and treatment costs avoided by preventing PPH, the cost per death averted is comparable to many other public health interventions. These cost estimates do not include the indirect costs associated with maintaining emergency transportation, blood transfer capacity, or surgical services, which would also be reduced by AMTSL. Nor do they capture the impact on women or their families of extra costs related to travel, reduced productivity related to post-PPH anemia, or family care provision for convalescent mothers.

It was noteworthy that with just a slightly higher rate of PPH (to 5%) AMTSL with oxytocin in ampoules becomes cost saving. At a rate of 8% (well below the rates reported in many countries and below the rate reported in many other districts in Viet Nam), AMTSL with Uniject devices is also cost saving. In a study of costs using data from Guatemala and Zambia and assuming a 10% underlying PPH rate and a 5% rate with AMTSL, AMTSL would save about $18,000 per 100,000 deliveries in Guatemala and over $145,000 per 100,000 deliveries in Zambia.[36] As noted earlier, the current study was not able to estimate the potential benefit that could be expected if Uniject also contributed to more widespread implementation of AMTSL (higher coverage) and more timely use for greater effectiveness.

In this study the rates of referral were lower than expected, with many women with PPH being successfully treated at CHC level, perhaps because of the highly experienced

midwives. In districts that did not have such expertise available at the CHC level, referrals would have been higher and cost savings associated with averted PPH episodes would have been even greater.

6.4 Limitations of study

There are several factors that limit the ability of this study to provide definitive evidence of the benefit of AMTSL. There was no way to blind participants to the intervention, and the study participants were not randomized, nor were the districts or smaller clusters within the districts. Since the study was placed within routine health services, it was not considered feasible to impose such randomization. However, without randomization it is possible to end up with non-comparable districts, as apparently happened with Thieu Hoa and Hoang Hoa.

The short duration of the study and the limited number of practice deliveries after training may have reduced the effectiveness of AMTSL in the hands of midwives in their first few months of experience with it. Inexperience with the new blood measurement technique and uneven supervision among the districts may have caused some misclassification of PPH and diluted the expected effects on PPH rates, which did not completely match the reduction in perceived need for PPH treatment. A longer study would overcome some of these limitations and reveal whether an even greater benefit could be achieved with AMTSL even in a setting with low PPH rates.

The costs used in this study were drawn specifically from the districts in Thanh Hoa province, which is densely populated and has better than average infrastructure. They did not involve start-up costs like training or indirect costs like facilities and other infrastructure. Data that was more representative of national average costs might have given a slightly different picture of the cost-effectiveness of these alternative strategies for managing third-stage labor. If midwives at primary level were less able to deal with hemorrhage and referral costs were higher in other settings, the cost of PPH treatment would be higher and the benefits of prevention would be greater.

7. Conclusions and recommendations

This is the first study to measure the effect of AMTSL in births in primary-level facilities in a low-resource country. In light of the global recommendations to adopt AMTSL wherever a skilled provider attends a delivery, it is important that the value of the technique is confirmed in a variety of settings. The study supports several important conclusions:

- AMTSL leads to measurable reduction in the rate of PPH, even when underlying rates are already low, and reduces the need for extra treatment such as bimanual compression, with its attendant risk of infection.

- AMTSL substantially shortens the third stage of labor, enabling the midwife to attend to other needs of the mother and newborn more quickly.

- Controlled cord traction conducted as part of AMTSL is not associated with an increase in retained placenta.

- The reduced incidence of PPH not only benefits women's health but also reduces the demand on the health care system in terms of financial resources, staff time, supplies, and

complex infrastructure.

- Midwives can easily learn AMTSL in a relatively short time, but putting it into practice using ampoules and standard syringes will be difficult sometimes in primary care facilities like CHCs where midwives often practice without any assistance.

- Use of Uniject devices overcomes many of the barriers cited by midwives with regard to the use of oxytocin in ampoules and will be less expensive than ampoules if prices at the lower end of the likely range become available.

This study, added to the rest of the international evidence base, confirms the value of active management of the third stage of labor in lower rates of PPH, shortening the duration of the third stage, and reducing the need to provide additional treatment. To implement routine use of AMTSL, the Ministry of Health will need to take the following steps:

- Include AMTSL in national policies and guidelines for all births attended by skilled attendants.

- Incorporate training in AMTSL into midwifery and medical courses and into refresher training sessions so that all midwives and doctors attending women at delivery have the necessary skills to provide this life-saving preventive measure.

- Immediately identify sources of oxytocin in ampoules with a full 10 IU dose, to avoid the need for busy midwives to open two ampoules.

- Consider adoption of oxytocin in Uniject devices when it becomes commercially available, based on its greater ease of use and time savings and its likely cost savings in Viet Nam more generally where PPH rates are assumed to be higher than the rates observed in this study.

With these interventions Viet Nam should be able to further reduce its maternal mortality ratio, of which PPH is a significant part, and move closer to the Millennium Development Goal of reducing maternal mortality 75% by 2015. By introducing this proven method of preventing life-threatening hemorrhage, hundreds of women's lives can be saved and thousands more can enjoy a healthy and satisfying childbirth without the debilitating consequences of postpartum hemorrhage.

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Appendix A. Detailed Methods

A-1. Study design

The study was designed with three main components to address key questions about acceptability and ease of use of Uniject, the effectiveness of AMTSL in reducing hemorrhage and its consequences, and the cost or cost savings involved in using AMTSL and oxytocin in Uniject. In a small fourth component, information was collected on the physical performance of the Uniject devices and any logistics barriers encountered.

User perceptions of acceptability among midwives already doing AMTSL. This descriptive component used baseline and post-intervention questionnaires with participating midwives in two districts where AMTSL is already routine practice. The primary outcomes of interest were midwife perceptions of acceptability and ease of use in three areas: Uniject devices as compared with standard syringes and ampoules, the practice of AMTSL, and the training materials. The intervention consisted of providing a brief training on the use of Uniject, orientation to a simple data collection form, and a supply of oxytocin in Uniject devices.

Effectiveness of AMTSL using either syringes or Uniject devices as compared to no AMTSL. This component used a quasi-experimental design to compare PPH rates and other outcomes in intervention and comparison districts. Introduction of a newly revised partograph was done in both intervention and comparison districts as a control measure and to ensure a reasonable benefit to the comparison districts for their participation. Midwives in both areas received refresher training on the estimation of postpartum blood loss, new blood collection containers with markings to help in estimation, and a supply of partographs. Midwives in the intervention district received training in AMTSL, use of Uniject, and use of a new partograph; a few days of delivery practice at a district or provincial hospital; orientation to data recording forms; and a supply of oxytocin-filled Uniject devices. Midwives in the comparison districts received training in use of the new partograph, a few days of delivery practice at a district or provincial hospital, and orientation to data recording forms.

The primary outcomes regarding effectiveness included PPH rates, duration of third stage, the need for additional treatment, and final maternal condition. Bleeding was considered as normal if it was measured at <300 ml; blood loss of 300-499 ml met the Vietnamese definition of PPH and was considered "high normal" for this study. Blood loss of 500-999 ml was considered moderate PPH, and loss of 1000 ml or more was considered severe PPH. Two cutoff points for longer third stage were considered: >15 minutes or >30 minutes. Treatment of excessive bleeding included doses of oxytocin or other oxytocic drugs, suturing, manual removal of the placenta, bimanual compression, intravenous (IV) fluids, transfusion, surgery, and referral. Final condition included healthy at discharge, ill at discharge, and death.

Cost or cost savings. This component involved the collection of actual and estimated direct costs in the project sites and modeling to project the cost or cost savings to the health system associated with routine use of oxytocin in Uniject compared to oxytocin in ampoules and to no AMTSL. The study was limited to costs from a health service

perspective and did not include patient out-of-pocket costs or social costs (patient or family member time). The primary outcomes included the direct cost of normal delivery without AMTSL, normal delivery at CHC with AMTSL (with ampoule and with Uniject), treatment of PPH at CHC and cost of referral to district hospital, and treatment of PPH at district and provincial hospitals. Direct costs include personnel costs, drugs and supplies, and equipment in providing these services. They do not include start-up costs associated with training.

Logistic and device performance. This descriptive component was based on prospective collection of data by midwives using Uniject devices and informal interviews with midwives, their supervisors, and managers of drug stores and distribution. Outcomes of interest were reports of defective Uniject devices and problems of distribution or storage of the devices.

A-2. Location and participants

The study was conducted in six lowland districts in Thanh Hoa province in the North Central Region of Vietnam, where safe motherhood activities had already been initiated and where provincial and certain district hospital staff had already been trained in AMTSL. All study districts were in the eastern part of the province close to the provincial city.

The acceptability study was carried out in Quang Xuong and Nong Cong districts, where health workers had already received training on AMTSL and were routinely practicing it before the start of this study. All CHC and district hospital midwives who had attended at least 20 deliveries (facility or home-based) in the preceding six months and expected to attend at least 20 in the study period (estimated at 40-45 midwives) were eligible to participate. The study was conducted over a two-month period from October through November 2004. In addition, midwives in Hoang Hoa district, which introduced AMTSL during the study, were asked about acceptability issues at the end, after ten weeks of experience with Uniject.

The effectiveness study was carried out in one intervention district (Hoang Hoa) and three comparison districts (Tinh Gia, Trieu Son, and Thieu Hoa). While it was originally planned to include a second intervention district (Nong Cong), it was discovered that they had started routine use of AMTSL by the time the study started, so Nong Cong was included in the acceptability study instead. Districts were selected on the basis of geographic and socioeconomic similarity and the number of births expected (sufficient to achieve the sample size in the available time). All district hospital and CHC midwives in the intervention and comparison districts were included in the effectiveness study, and all consecutive mothers (18 years and older, whether at home or in a facility) completing second stage of labor vaginally (and therefore suitable for AMTSL) while under the care of participating midwives during the study period of July through November (comparison) or December 15 (AMTSL) were eligible for enrollment.

Accurate data on the incidence rate of PPH are not available for Vietnam, or for Thanh Hoa specifically. Although the REDUCE-ALIVE report estimated the national incidence at 11.3%,[1] recorded figures from recent years prior to the study suggested much lower

[1] Academy for Educational Development. Assumptions and estimates for the application of the REDUCE–ALIVE advocacy model to reduce maternal mortality and improve newborn survival in Viet Nam.

rates in Thanh Hoa (less than 1%). Since that rate seemed to indicate serious under-reporting, we used an estimated baseline rate of 5%, an assumed 40% decline associated with AMTSL to 3%, a 95% one-sided confidence interval with 80% power, and a 1:2 matching scheme to calculate the necessary sample size of 985 in the intervention (AMTSL) group and 1,970 births in the comparison group (Epi Info 6.04). Since the PPH rate during the initial months of the study was smaller than the level used in this initial sample size calculation, the study was extended to increase the sample size; at a baseline PPH rate of 4% and using a 1:2 matching scheme, it was determined that 1,241 births in the intervention district and 2,482 births in comparison districts would be needed.

Cost data were gathered from a sample of two commune health centers (CHCs) and the district hospital in each of four districts (two from the acceptability study and two from the effectiveness study districts) in December 2004, as well as in the Thanh Hoa Obstetric and Gynecology Hospital.

Logistics data were gathered in all districts where Uniject devices were used.

A-3. Measurement of blood loss, definition of AMTSL, and recommended management of PPH

After delivery of the newborn, a plastic drape was placed under the woman's hips so that blood could be channeled into a tray placed at the foot of the delivery table. After completion of the delivery, the tray was emptied into a smaller plastic cylindrical basin which had markings drawn on at 300 ml, 500 ml, and 1000 ml. In most home deliveries, midwives also used the plastic drape, placed the tray under the bed, and then used the basin to measure the blood.

The study sites followed a modified version of the protocol for AMTSL previously used in the Quang Xuong NGO Networks for Health Safe Motherhood project training protocol. The final protocol, approved by the MOH and used in the training, included:

- Routine intramuscular (IM) injection of 10 IU of oxytocin within two minutes after the birth.
- When the uterus is contracted, exertion of controlled cord traction with one hand while the other hand is placed above the pubis to guard the uterus.
- Uterine massage to stimulate contractions.

Although it was not part of the official protocol, immediate cord clamping was also taught during the training.

Recommendations for management of PPH were dependent on the setting.

- The first response to excess bleeding was a second dose of oxytocin (or first dose if prophylactic oxytocin had not been used).
- In CHC or home delivery where PPH due to uterine atony persists after a second dose of oxytocin, apply bimanual compression of uterus; if still persisting after this, refer promptly to nearest hospital for further care.

REDUCE-ALIVE Workshop in Viet Nam, April 2002. Washington DC: Academy for Educational Development, 2002.

- In CHC or home delivery where PPH persists after suturing of lacerations or removal of placenta or fragments, refer promptly to nearest hospital for further care.
- In district hospital, if uterine atony persists after second IM dose of oxytocin, establish IV line and give IV Ringer's Lactate 500 cc + 10 IU oxytocin full flow. Doctor should provide further management as needed.

Disposal of Uniject devices was to be done in the same manner as disposal of used syringes, depending on the location. All midwives were cautioned not to recap used devices, since this increases the risk of needle-stick injury.

A-4. Training

The training team consisted of experienced obstetricians and midwives from national and provincial levels of the MOH and resource staff from PATH. For the acceptability study, midwives in Quang Xuong district attended a half-day training that included an orientation to the study, explanation and demonstration of the Uniject device, explanation of the data forms and informed consent process, role-play of the consent process, and practice activating and injecting two to three Uniject devices. Midwives in Nong Cong went through the full training for the effectiveness study (described below), which included all the elements covered in Quang Xuong, before they were switched to this component of the study.

For the effectiveness study, 54 midwives in the intervention district attended four days of training, which included 1.5 days of classroom work and 2.5 days at the district and provincial hospitals for clinical practice. The theoretical work covered an orientation to the study, a detailed explanation of AMTSL and other elements of immediate postpartum care, use of Uniject devices, use of the new partograph, recognition and management of PPH, data recording on the study forms, and the informed consent process. Midwives practiced activating and injecting Uniject devices and did role-play to practice the consent process. In the following days, they observed and participated in deliveries using the new partograph and the AMTSL and blood measurement techniques (using ampoules and standard syringes, since Uniject devices with oxytocin were not available yet). Although the target was for each midwife to conduct five supervised deliveries during the training period, there were not enough deliveries occurring at the hospitals, so most midwives had conducted only one to three supervised deliveries using the new techniques and had observed a few others.

Midwives (142) in the comparison districts of the effectiveness study attended two days of training, one for classroom work and one for clinical practice. The theoretical work covered an orientation to the study, an explanation of the new partograph, recognition and management of PPH, data recording on the study forms, and the informed consent process. The second day was spent conducting and observing labor using the new partograph and deliveries using the new blood measurement techniques.

A-5. Materials

Uniject is a non-reusable device consisting of a plastic blister with a drug reservoir and a neck to which a needle is permanently attached by means of a hub (Figure 1). A membrane between the neck and the reservoir seals the device and maintains the sterility of the solution. After removal from its foil packet, the device is activated by bringing the needle cap and the blister together with a simple pushing action; this forces one end of the needle through the membrane so that it reaches the reservoir. After removing the plastic needle cap, the needle is inserted into the injection site with a downward motion and the drug is then injected by squeezing the reservoir until it collapses. A small amount of drug remains in the reservoir, but the device is slightly overfilled to compensate for this. The device has a one-way valve that prevents refilling.

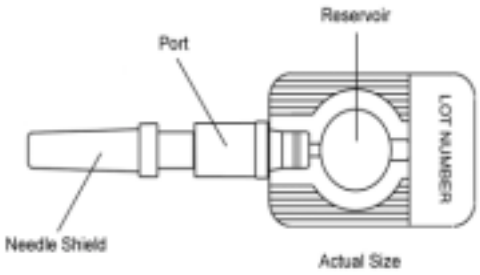

Figure 1. Uniject Injection Device

For this study, Uniject was filled with sufficient oxytocin to ensure a dose of 10 International Units (IU). The device was provided by a pharmaceutical company in India that currently manufactures and exports oxytocin in ampoules. Appropriate certificates of manufacturing quality and stability information on the trial batch were provided to Vietnamese drug regulatory authorities, which approved its use. Extra devices filled with saline were provided for practice during training.

Oxytocin-filled Uniject devices were kept outside the cold chain at CHC level, usually in a medicine cabinet, and returned to the district hospital for refrigerated storage and use if not used within two months. Those used at the district hospital were kept refrigerated until they were used.

Trays and marked basins for measuring blood loss were provided to all facilities in the effectiveness study districts.

Partographs were provided by the MOH. Although partographs have been used in training programs in Vietnam since the early 1990s, there were several different versions being used. After testing and gathering local experience, the MOH has recently standardized the partograph based mainly on the current WHO format.

A-6. Data collection and analysis

A-6.1 Acceptability study

Data collection. Baseline and post-intervention questionnaires were completed by midwives in the two acceptability study districts at their monthly meetings at the district hospital. Additional information on acceptability was collected from midwives in the effectiveness study districts through a similar questionnaire after completion of patient enrollment. The baseline questionnaire collected information on the knowledge of participating midwives about AMTSL; use of oxytocin (timing and dose); use or reuse of

syringes or needles; sterilization of reused syringes; experience with ampoules and standard syringes; participation in home deliveries; and background information on age, midwifery training, and years of midwifery experience.

The post-intervention questionnaires had several common questions for everyone and then different modules for those who were already experienced with AMTSL, those who began using it in the intervention area, and those in the comparison districts who did not do AMTSL. All midwives in the effectiveness study answered questions about ease of use of the partograph; any difficulties recognizing PPH; participation in home deliveries; whether syringes are ever reused; and background information on age, midwifery training, and years of midwifery experience. Midwives with Uniject experience were also asked questions about ease of use of the device in comparison to other syringes, problems with AMTSL, functional problems with Uniject, and the instruction sheet.

Data management and analysis. Data were entered using Epi Info and were analyzed using SPSS (SPSS Inc, Chicago, USA). Closed-ended questions were analyzed with simple frequencies and bivariate analysis. Open-ended questions were reviewed by two researchers familiar with the issues, to determine appropriate categories and coding for analysis. Typical comments were noted and have been included as illustrative quotations.

A-6.2 Effectiveness study

Data collection. All midwives completed a Monthly Delivery Outcome Record that included basic information about each eligible delivery: woman's age and parity, category of blood loss estimated (normal, high normal, moderate PPH, severe PPH), cause of PPH, any action taken (first or second dose of oxytocin, other drugs, suturing, manual removal of placenta, referral, etc.), and estimated length of third stage (1-5 minutes, 6-15 minutes, 16-30 minutes, >30 minutes). Those doing AMTSL were also asked about the practice of controlled cord traction, early clamping of the cord, each Uniject dose used (noting comments on any defective devices identified), and how they disposed of used devices.

It was planned to track the baseline PPH rate in the intervention district in the period after training, but before the Uniject devices became available, to determine whether the PPH rates in the intervention and comparison districts were similar at the start. However, midwives in the intervention district initiated the practice of AMTSL using standard ampoules and syringes immediately after training, preventing the establishment of the baseline rate.

Basic clinical information was collected on all cases of PPH referred to district or provincial hospitals from the intervention and comparison districts to ascertain condition on arrival at referral hospital (pulse, blood pressure, pallor, and consciousness), treatments provided, and final outcome. Similar information on treatments was collected for women who were not referred but experienced PPH in the hospital.

Data management and analysis. Data were entered into a database created in Epi Info with double entry of effectiveness data and appropriate data checks. Analysis was based on which district a woman was in, regardless of whether she actually received the intervention or not (known as "intention to treat" or effectiveness rather than efficacy), although additional analyses were undertaken to determine whether outcomes were similar according to actual interventions received. Bivariate analyses of categorical variables were evaluated using chi square statistics. Unconditional multiple logistic

regression was conducted using SPSS to adjust for confounding factors. Relative risks approximated by the odds ratios were estimated by the method of maximum likelihood, and 95% confidence intervals (CI) were based on the standard error of the coefficient estimate and the normal approximation.

A-6.3 Cost study

Data collection. Based on consultation with clinicians, component cost categories of staff, equipment, supplies, and infrastructure were identified for normal deliveries with and without AMTSL, with standard syringes and Uniject devices, and for PPH treatment for moderate and severe cases at CHC, district hospital, and provincial hospital. Resource use (type and quantity of labor, drugs, supplies, and equipment) was verified by reviewing sample records of specific cases of each type and by interviewing doctors and midwives at each level, and expenditure data on inputs were collected from financial records at each type of facility. Total staff revenues data (salary plus all other allowances and bonuses—hereinafter called salary) were obtained from facility records. Some unavailable costs of equipment were estimated using central prices.

Data management and analysis. Data were entered into Excel spreadsheets and were used to generate per case costs (from a health services perspective). Using those costs and data generated by the effectiveness study on the frequency of various clinical outcomes, the cost or cost savings associated with AMTSL and with ampoules compared with Uniject devices was calculated. Since oxytocin in Uniject is not yet commercially available, a price of US$0.50 was assumed for the primary analysis. A simple sensitivity analysis was conducted to test the effect of different Uniject prices ($0.40, $0.75) and of different PPH rates.

A-7. Ethical review

The study protocol was approved by the Scientific Committee of the MOH in Vietnam, the Columbia University Institutional Review Board, and PATH's Human Subjects Protection Committee. Participation in the acceptability and cost studies was strictly voluntary, and questionnaires were filled in without identifiers. In the effectiveness study, documented informed consent was obtained from all women, usually during a third-trimester antenatal visit but occasionally during the first stage of labor. Women in the AMTSL district signed a detailed written informed consent after counseling. Women in the comparison districts gave their oral consent to have their data included in the study, which was noted in their charts.

Appendix B. Additional Results

B-1. Description of midwife participants

A total of 216 midwives in six districts participated in the study, of whom 87 in three districts completed post-intervention questionnaires about their experience with AMTSL and Uniject devices. Midwives in the three comparison districts tended to be younger (18-29 years) and less experienced than midwives in the AMTSL districts, but the types of training were generally similar (Table B-1). Only 36 of the original 52 midwives in the acceptability study districts completed the post-intervention questionnaire because the others were on duty at the time of the post-intervention meeting, but their characteristics were similar to the whole baseline group except for a smaller proportion of those with Assistant Doctor training.

Table B-1. Description of midwife participants

Variables	Acceptability Districts				Effectiveness Districts			
	Baseline No. (%)		Post-Intervention No. (%)		AMTSL No. (%)		Comparison No. (%)	
Total	52*		36**		51		113	
Age:								
18–29	10	(19.2)	6	(17.1)	3	(5.9)	29	(27.5)
30–49	38	(73.1)	27	(77.1)	46	(90.2)	78	(69.0)
50–59	4	(7.7)	2	(5.7)	2	(3.9)	6	(5.3)
Working experience:								
< 5 years	11	(21.2)	6	(16.7)	2	(3.9)	25	(22.1)
5–9 years	16	(30.8)	12	(33.3)	22	(43.1)	27	(23.9)
10–29 years	24	(46.2)	17	(47.2)	27	(52.9)	60	(53.1)
Ó30 years	1	(1.9)	1	(2.8)	0		1	(0.9)
Midwife training level:								
Primary	1	(2.0)	1	(2.8)	1	(2.0)	0	
Secondary	19	(37.3)	21	(58.3)	21	(41.2)	52	(46.)
Assistant doctor	31	(60.8)	14	(38.9)	29	(56.9)	58	(51.2)
Others	0		0		0		3	(2.7)

*Data missing on training level for 1; **Data missing on age for 1

B-2. Additional acceptability and ease of use results

Only one midwife reported using the wrong dose (5 IU) for AMTSL at baseline, while all others reported using 10 IU. Similarly, only one midwife reported ever reusing standard disposable syringes; she said she used the syringes just twice but did not give clear information on how she prepared them for reuse.

During the two-month intervention period, midwives in Quang Xuong and Nong Cong used about 400 Uniject devices while midwives in Hoang Hoa used about 650. On

average each midwife used about 11-12 devices, but 6% in Quang Xuong and Nong Cong used fewer than 5 devices, and 10% in Hoang Hoa used fewer than 5. Based on this experience, 98% answered that Uniject devices were easier to use than standard syringes (the remaining 2% said they were the same). The main reason given was convenience.

Similarly, all 87 midwives said they preferred using Uniject devices over ampoules and standard syringes. Again, convenience was the predominant reason mentioned by more than 60% of all midwives; ease of use was mentioned by more than half, and being faster was mentioned by nearly 20% of the midwives in Hoang Hoa. Less common responses were that it was effective (3), did not waste medicine (3), caused quicker expulsion of the placenta (2), reduced blood loss (2), was safe (2), reduced needle accidents (1), was easy to store (1), and was free (1). Almost all (97.6%) rated it easy to activate and inject with Uniject devices, while two midwives found it moderately difficult to activate and three found it moderately difficult to inject. One said that she found it difficult to activate at first, but she later had no problem with it. About 20% of midwives reported that mothers mentioned less or no pain at the injection site and less bleeding, and about 15% said that mothers mentioned that the placenta was expelled more quickly, but it is not known how commonly these remarks were made.

Measuring blood loss. All midwives in the effectiveness study were asked about the new way of measuring blood loss. Nobody found it "very difficult" to do, but significantly more midwives in Hoang Hoa reported it as somewhat difficult than those in the comparison districts (31.4% versus 12.4%, $p < .01$). The types of difficulties mentioned included the extra actions needed to change the tray and pour the blood into a separate container for measuring, especially when they were practicing alone. As one midwife said: *"It (measuring blood loss) is little bit difficult because there was only me on duty, so I had to work hard. If there were two persons, it was easier."*

New partograph. Most midwives found the new partograph easier to use (74%), while 17% rated it about the same as the older one. A few (2%) found it more difficult to use, while the rest (7%) had not used the old one before.

B-3. Additional effectiveness results

Description of mothers and deliveries. A total of 3,607 eligible women were included in the study. Women in the AMTSL and comparison districts differed somewhat on key characteristics (Table 3 in main report). Women in the comparison districts were almost twice as likely to be young (18-19 years old) and were somewhat more likely to be having their first delivery, while mothers in the AMTSL district were somewhat more likely to be grand multiparous (three or more prior deliveries). Less than 1% of all mothers had four or more prior deliveries. While home births were just a small proportion in both groups, a much higher proportion of comparison group births occurred in the district hospitals (25% versus 11%) instead of the communal health centers. Although the proportions were small, mothers in the comparison districts received oxytocin for augmentation in the first stage of labor more often than did mothers in the AMTSL district. The differences in age, place of delivery, and parity were statistically significant, but stage one differences were not.

Distribution of preventive postpartum oxytocin and AMTSL. More than 95% of women in the intervention district received all three components of AMTSL (10 IU of preventive

oxytocin, uterine massage, and controlled cord traction); a few did not receive any oxytocin and about 2% received only one ampoule of 5 IU (Table B-2). About half the oxytocin was administered by Uniject devices and the rest by standard syringes. In the comparison districts a few women received a dose of 5 IU of preventive oxytocin; 75% of these were at a district hospital. Because most women received the intervention they were supposed to receive based on their district, the analysis was done by intervention and comparison group assignment rather than by whether an individual received all components or not (also known as "intention to treat" analysis).

Table B-2. Implementation of AMTSL

	AMTSL		Comparison	
	No.	%	No.	%
Total	1,236	100.0	2,371	100.0
Preventive oxytocin				
None	31	2.5	2,339	98.7
5 IU ampoule	22	1.8	32	1.3
10 IU ampoule	571	46.2	0	0
10 IU Uniject	612	49.5	0	0
Cord traction	1,223	99.0	0	0
AMTSL	1,177	95.2	0	0

Bleeding outcomes. PPH of 500 ml or greater was less common in the AMTSL district than in the comparison districts (3.4% versus 4.3%). Although the unadjusted relative risk (RR) for hemorrhage Ó500 ml suggested a protective benefit of 22% for AMTSL (RR 0.78; 95% CI: 0.55, 1.1) that was not statistically significant, subsequent multivariate analysis showed a stronger and statistically significant protective effect. Severe PPH was rare and could not be evaluated statistically. The protective relationship was very similar for PPH specifically due to atony, suggesting that reduction of atony was the primary reason for the benefit seen. The rates of retained placenta were very similar in the two groups, with no apparent effect due to the use of controlled cord traction. The overall rate of retained placenta was identical in the two groups (0.9% each). The rate of tears and lacerations was somewhat lower in the AMTSL group, but it was not statistically significant (RR 0.55; 95% CI: 0.22, 1.4). The effect of AMTSL in shortening the third stage of labor was dramatic, reducing the number with a third stage greater than 15 minutes by 88% (RR 0.12; 95% CI: 0.09, 0.15) and those with a third stage greater than 30 minutes by 77% (RR 0.23; 95% CI: 0.13, 0.41).

Bleeding rates were higher for certain subgroups, such as older mothers, women with three or more previous deliveries, and those receiving oxytocin in first-stage labor in Hoang Hoa (Table B-3). Among the 103 women with parity of five or more, none had PPH in the AMTSL district, while 15% did in the comparison districts. Rates were also higher for women delivering in the hospital, especially in Hoang Hoa, but the difference was small (data not shown) once women with first-stage augmentation (done mostly in hospitals) were removed. Since these groups were not equally represented in the two groups, these potentially confounding variables were included in the logistic regression models to adjust for their effects.

Table B-3. PPH rates for subgroups

	AMTSL		Comparison	
	No.	%	No.	%
Total	1,236	100.0	2,371	100.0
PPH Ó500 ml				
18–34 years	38	3.3	83	3.8
Ó35 years	4	4.9	20	11.7
Parity 1–3	38	3.2	92	4.0
Parity 4–7	4	7.0	10	13.7
Oxytocin Stage 1 – no	34	2.8	99	4.3
Oxytocin Stage 1 – yes	8	27.6	4	5.0
PPH due to atony				
18–34 years	27	2.3	56	2.5
Ó35 years	2	2.5	15	8.8
Parity 1–3	25	2.1	63	2.8
Parity 4–7	4	7.0	7	9.6
Oxytocin Stage 1 – no	24	2.0	69	3.0
Oxytocin Stage 1 – yes	5	17.2	2	2.5

Treatment outcomes. AMTSL resulted in a 40% lower use of treatment interventions. In this study, women were referred for higher level care only rarely. Altogether only 12 women (0.3%) were referred to a higher level facility, and none of these was for PPH due to atony. Of the four due to PPH, three had retained placenta and one was recorded as "other." Of the 21 cases of severe PPH, 13 (62%) were due to atony; six of these occurred at CHCs and were managed there without referral, while the others occurred in a district hospital. Intravenous (IV) fluid was used in two cases of retained placenta.

During the study period there was one maternal death. One woman in her thirties, on her third delivery, experienced PPH due to atony despite AMTSL after an induced labor augmented with oxytocin. Although she was in a hospital attended by an experienced physician, received additional oxytocin, aortal compression, and several units of blood, she died in less than two hours after the onset of her hemorrhage (late at night) before surgical intervention could be organized.

Unanticipated district differences. Although Thieu Hoa reported much lower rates of PPH for both atony and retained placenta, they reported similar or higher duration of the third stage of labor and of use of treatments like additional oxytocin and bimanual compression (Table B-4). In fact, they were more likely to administer oxytocin for women with high normal blood loss (Ó300ml) (30%) as compared with Tinh Gia (15%) or Trieu Son (24%). The management of first stage of labor also seemed to be different in Thieu Hoa, which had slightly more young mothers but a comparable number of first-time mothers, and yet used oxytocin to augment first-stage labor much less often. Historically, the annual PPH rate reported in Thieu Hoa (using the national cutoff of 300 ml, but based on clinical estimation) has been between 3.3% and 3.5% since 1999. Based on the rates

reported below using the 300 ml cutoff and actual measurement, it appears the earlier rates represented some substantial underestimation of PPH.

Table B-4. Unanticipated differences among comparison group districts

	Tinh Gia		Thieu Hoa		Trieu Son	
	No.	**%**	**No.**	**%**	**No.**	**%**
PPH Ó300 ml	203	26.1	125	14.4	122	16.9
PPH Ó500 ml	47	6.0	25	2.9	31	4.3
PPH atony	29	3.7	17	2.0	25	3.5
Retained Placenta	8	1.0	0	0	2	0.3
3rd stage duration >15 mn	425	55.0	437	50.8	236	33.0
3rd stage duration >30 mn	49	6.3	43	5.0	16	2.2
Any PPH oxytocin given	60	7.7	52	6.0	52	7.2
Bimanual compression	20	2.7	35	4.1	42	5.9
Oxytocin Stage 1	32	4.1	1	0.1	47	6.5

In an attempt to explore whether the study districts were similar in reported PPH rates before the study began, district records were reviewed for the period April through October 2003 (Table B-5). Only PPH cases occurring in deliveries attended by government midwives were included in the count, and the different types of PPH were also recorded. This was prior to the training on measuring blood, when blood loss was only estimated clinically, and PPH was considered as blood loss of 300 ml or more.

Table B-5. Historical general and type-specific rates of PPH, October 2003–April 2004

	Hoang Hoa		Tinh Gia		Thieu Hoa		Trieu Son	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Total deliveries	2,452	100.0	1,792	100.0	1,783	100.0	1,543	100.0
PPH Ó300 ml	247	10.1	141	7.9	22	**1.2**	57	3.7
PPH atony	91	3.7	52	2.9	2	**0.1**	18	1.2
Retained placenta	67	2.7	51	2.8	1	**0.1**	18	1.2
Tears	81	3.3	37	2.1	19	1.1	19	1.2
Other	8	0.3	1	0.1	0	0	2	0.1

Hoang Hoa and Tinh Gia apparently started with higher rates of PPH both generally and specifically due to atony, while Thieu Hoa reported a very low rate of PPH from all causes. In particular, while atony accounted for about one-third of all PPH in the other three districts, it accounted for only 9% in Thieu Hoa. No explanations for this unusual pattern could be identified, but both the higher starting rate in Hoang Hoa (the AMTSL district) and the very low rate in Thieu Hoa (comparison district) may have contributed to the appearance of a smaller than expected effect of AMTSL.

Multivariate analysis of effectiveness of AMTSL. Multivariate logistic regression analysis makes it possible to adjust for the effects of extraneous factors while identifying the

specific risk associated with the intervention. The key outcomes of interest for multivariate analysis were overall PPH rates (Vietnam definition of Ó300 ml and international definition of Ó500 ml), PPH of Ó500 ml due to atony, duration of third stage, need for treatment doses of oxytocin, and need for bimanual compression. These were examined based on "intention to treat," since there was little crossover of intervention (that is, most in the AMTSL district received all elements and very few in the comparison districts received any prophylactic oxytocin). The models included age (Ó35 years), parity (Ó3 prior births), place (hospital vs. CHC/home), and first-stage augmentation as confounders. The odds ratio (OR) was used as an approximation for the relative risk, using the comparison districts as the reference category for the outcomes.

Appendix C. Additional Costing Methods and Results

C-1. Data sources and assumptions

Direct costs for salaries, supplies, and equipment and time estimates were based on information provided in the study districts. Time and supplies associated with first stage of labor and postpartum home care were not included. Although repair of perineal and other tears adds about VND 12,000 to CHC costs and about VND 16,000 to district hospital costs, they are not included in any of the cost models, since they are unlikely to vary across different strategies. Where it has been used on a pilot basis, women have themselves often paid for the oxytocin, but it was included as a health service cost here. The cost of oxytocin in ampoules was VND 6,000 for two 5 IU ampoules, and VND 500 for a disposable syringe and needle. The oxytocin-filled Uniject devices were donated for the study. Since these are not yet commercially available, the unit cost was estimated at US$0.50 (VND 7,950). The exchange rate used throughout is (2005) US$1 = VND 15,900. Treatment for moderate PPH was costed as requiring extra drugs, supplies, and time, but no transfusion. Treatment for severe PPH was assumed to require all that plus transfusion, but no surgery. Treatment for very severe PPH was assumed to require both transfusions and surgery. In the base case it was assumed that 10% of the severe PPH cases required both transfusions and surgery.

C-2. Base model of delivery and PPH treatment costs

Although the costs for treatment at provincial level were calculated, they are not included in the base case since there were no instances of such referral during this study. Where such transfers do occur, those costs would be additional to the costs already incurred at the district hospital if the woman went there first. In the same way, the district hospital costs of treating referred women were added to the costs already incurred at the CHC for women treated at both places.

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