

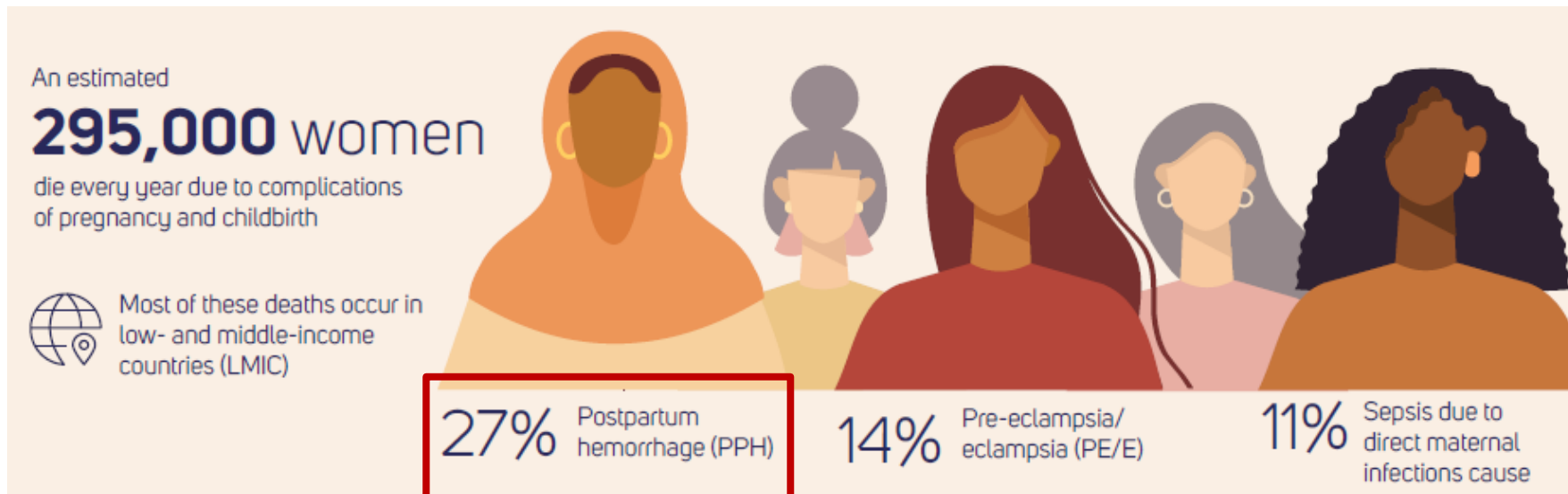
WHO Recommended Uterotonics for PPH and SDG 3.8

- . do women in LMIC have access to effective and quality uterotonics?*
- . which are the barriers for implementing the WHO recommendations?*

Mariana Widmer
WHO/SRH/MPH



PPH is the 1st cause of maternal mortality



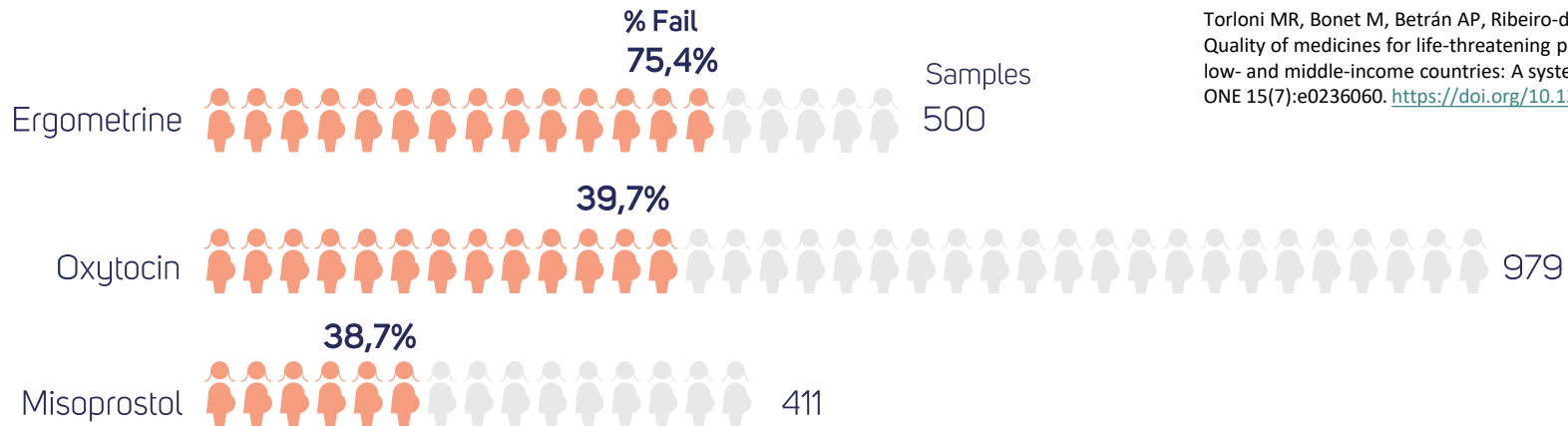
- Most **PPH-associated deaths** could be **avoided** using **prophylactic UTEROTONICS** during the third stage of labour, and **appropriate treatment**.
- **ACCESSIBILITY** and **SUSTAINABILITY** of **GOOD QUALITY UTEROTONICS** in **LMIC** must be ensured to achieve Universal Health Coverage.

Good quality = comply with specifications as per Pharmacopoeia referenced

There is a widespread problem with the quality of uterotonics used in LMIC to manage PPH.

PLOS ONE

Torloni MR, Bonet M, Betrán AP, Ribeiro-do-Valle CC, Widmer M
Quality of medicines for life-threatening pregnancy complications in low- and middle-income countries: A systematic review. 2020 PLoS ONE 15(7):e0236060. <https://doi.org/10.1371/journal.pone.0236060>



- Access to quality medicines is a **Human Right**.
- Access to medicine is one of the fundamental elements in achieving the right of everyone to the enjoyment of the highest attainable standard of health.

WHO Recommendation – PPH prevention

In settings where multiple uterotonic options are available, **oxytocin (10 IU, IM/IV) is the recommended uterotonic agent for the prevention of PPH for all births.**



- Vaginal birth or caesarean section
- Skilled health personnel required
- **Good quality oxytocin**

Choice of uterotonics for PPH prevention	2. In settings where multiple uterotonic options are available, oxytocin (10 IU, IM/IV) is the recommended uterotonic agent for the prevention of PPH for all births.	Recommended
	3. In settings where oxytocin is unavailable (or its quality cannot be guaranteed), the use of other injectable uterotonics (carbetocin, or if appropriate ergometrine/methylergometrine, or oxytocin and ergometrine fixed-dose combination) or oral misoprostol is recommended for the prevention of PPH.	Recommended

When oxytocin is likely to be of substandard quality?



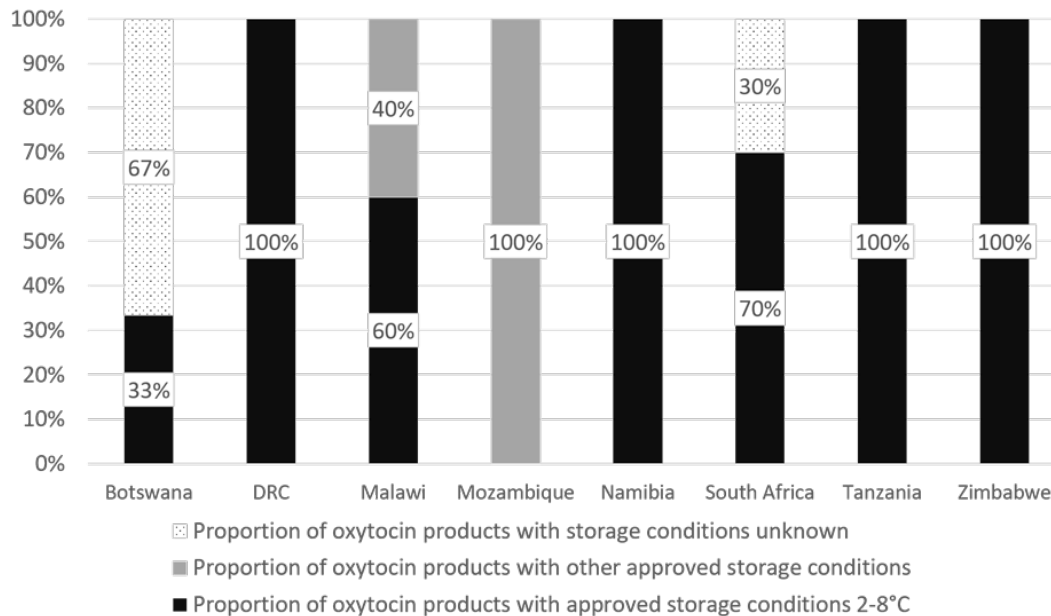
- ❑ The oxytocin is not WHO prequalified or is not registered by a recognized regulatory authority,
- ❑ the oxytocin is not labelled for storage at 2°- 8°C, or
- ❑ the oxytocin is not kept at 2°- 8°C.

Health systems' stakeholders need to ensure that the manufacture and cold-chain transport and storage of oxytocin is sufficiently rigorous to ensure good quality.

WHO/HRP/RPQ SADC survey

- Registered oxytocin is labelled for outside the cold chain.
- Products labelled for cold storage are kept outside the fridge.

Storage conditions of registered oxytocin products in SADC countries



Stability profiles of oxytocin labelled for $\leq 25^{\circ}\text{C}$ storage offer **NO** stability advantage over those labelled for $2^{\circ}\text{-}8^{\circ}\text{C}$.

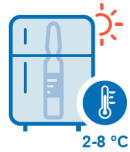
(BMJ Open 2019;9:e029083)

Oxytocin has to be transported and stored at 2°-8°C



WHO/UNICEF/UNFPA JOINT STATEMENT

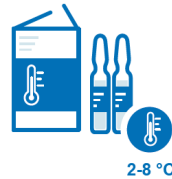
Appropriate Storage and Management of Oxytocin – a Key Commodity for Maternal Health



Ensure that oxytocin is managed in the **cold chain (2-8°C)**



Procure oxytocin that meets **quality requirements** established by WHO or regulatory authority recognized by WHO



Label oxytocin to clearly indicate storage and transport at **2-8°C**



Kit with oxytocin



<https://www.who.int/publications/item/9789240022133>

WHO/PQT: medicines | Guidance Document 29 October 2018

OXYTOCIN INJECTION

Clarification of stability data and storage statement requirements

Oxytocin, indicated for prevention and treatment of postpartum haemorrhage, is a lifesaving medicine. Recent and past surveys undertaken by WHO and others have revealed that a significant number of samples of oxytocin injection collected from the market contain unacceptable levels of the active ingredient and related substances^{1,2}. These non-compliant products, usually found in high ambient temperature countries, are of particular concern given the high risk of treatment failure.

Based on the survey results, PQT Medicines (PQT-m) experts are of the opinion, that the main reason for the non-compliant assay and related substance levels observed in samples collected from the field appears to be inappropriate storage of the products out of refrigeration. This happens either due to failure to observe the labelled storage conditions or inappropriate labelling of the products with statements allowing long term storage or short term excursions out of refrigeration.

PQTm understands that the product is used at primary health care facilities or higher health institutions where facilities to store the product at the required storage condition of 2-8°C throughout the product shelf life should be available. PQT-m also recognises that statements on short term excursions may be confusing and may therefore contribute to unregulated excursions. For these reasons, PQT-m has not been accepting oxytocin injection applications that propose long term storage out of 2-8°C or those that propose short term excursions out of the long term storage condition of 2-8°C.

This notice is issued to clarify the required stability data and storage statement for prequalification of oxytocin injection products.

Stability data requirement

The required long term stability study condition for prequalification of oxytocin injection is 5°C ± 3°C. Consequently, the accelerated stability studies should be conducted at 25°C or higher. At the time of submission, at least six months accelerated and six months long term data should be included in the submitted dossier.

In addition, to account for potential water loss, for products packaged in plastic ampoules (semipermeable containers), the accelerated stability study should be conducted at low relative humidity conditions (i.e., at 40%RH or lower). Alternatively, as described in the WHO and ICH stability guidelines, the applicant can perform the stability studies under higher RH and calculate the water loss at the low RH.

¹ Survey of the Quality of Medicines Identified by the UN Commission Life-Saving Commodities for Women and Children. Geneva: World Health Organization, 2015.

² Toroni M, Gomes Freitas C, Karagül U, Meiri Gülmescioğlu A, Wimmer M. Quality of oxytocin available in low- and middle-income countries: A systematic review of the literature. BJOG: An International Journal of Obstetrics and Gynaecology 2018

























Substandard oxytocin - consequences

- Substandard oxytocin represents a barrier for WHO recommendations.
- Women could be at higher risk of having PPH.
- Women could be at higher risk of having a CS.
- Women at risk of receiving an overdose of oxytocin.

Systematic Review on Perception of healthcare providers about the quality of oxytocin available in their settings (*under preparation*).

Nigeria, 2017 (77% private health facilities)	Nigeria, 2019 (52% public health facilities)
13% of health personnel perceived substandard quality	21 % of health personnel perceived substandard quality
5% double the dose	37% double the dose
45% change to another medicine	54% change to another medicine
3% do caesarean section	57% CS
5% do not report	64% do not report

WHO PPH prevention Recommendations – Summary

Context			Uterotonics recommended for PPH prevention To effectively prevent PPH, only one of the following uterotonics ^a					
			Oxytocin 10 IU (IV/IM) 	Carbetocin ^b Carbetocin ^d 100 µg, IM/IV  HS carbetocin ^e 100 µg, IM/IV 		Ergometrine ^c 200 µg, IM/IV 	Oxy-ergo ^c 	Misoprostol 400 or 600 µg 
All recommended uterotonics available	Skilled health personnel available	Oxytocin, ergometrine and oxy-ergo stored continuously in the cold chain	 First choice					
		Fragile cold chain system						
	Skilled health personnel not available	-						

^a uterotonics need to meet quality requirements established by WHO or a regulatory authority recognized by WHO.

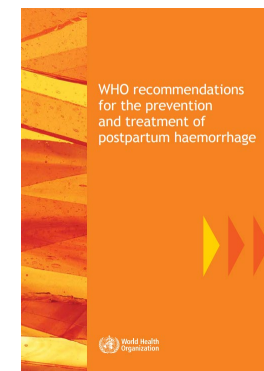
^b in contexts where its cost is comparable to other effective uterotonic.

^c in contexts where hypertensive disorders can be safely excluded prior to its use.

^d Storage conditions: 2-8°C

^e Storage conditions: 30°C

WHO recommendations – PPH treatment



PPH Treatment						
Uterotonics					Other	
Oxytocin	Carbetocin HS carbetocin	Ergometrine*	Oxy-ergo*	Misoprostol	Tranexamic acid	Isotonic crystalloids
✓	✗	✓	✓	✓	✓	✓

**in contexts where hypertensive disorders can be safely excluded prior to its use.*

WARNING

TXA injection medication errors.

Proposed solutions:

- revising the TXA injection container labels and carton labelling to highlight the recommended intravenous route of administration;
- strengthening the warnings in the TXA prescribing information to include the risk of medication errors due to incorrect route of administration.

WHO PPH recommendations - Implementation barriers

SUSTAINABILITY

SUPPLY

Lack of quality PPH drugs throughout health systems

INNOVATIONS

Lack of data to support new indications

ACCESSIBILITY

. Irregular last mile distribution.

. Low uptake of new products due to limited stakeholder awareness and knowledge.

. Hurdles common to early product introduction (Reg approvals)

ADOPTION

Lack of updated national PPH policies and guidelines

- Oxytocin is the 1st choice uterotonic for PPH prevention and treatment, however, there are still oxytocin products labelled for storage at 25°C
 - ⊘ Oxytocin of substandard quality
- HSC is a recommended alternative to oxytocin, however it is indicated only for PPH prevention
 - ⊘ HSC cannot be used for induction/augmentation nor PPH treatment
- Ergometrine or misoprostol which are indicated for induction, PPH prevention and treatment
 - ⊘ Ergometrine and misoprostol of substandard quality
 - ⊘ Ergometrine is not indicated for women with hypertension
- TXA is part of the 1st response PPH treatment package
 - ⊘ TXA of substandard quality
 - ⊘ Misuse, medication error
- WHO PPH recommendations and living guidelines update
 - ⊘ Lack of updated national PPH policies and guidelines

Implementation barriers – potential solutions

- **RAISING AWARENESS**
- **INFORMING**
- **TRAINING**

- Quality medicines
- Proper storage and disposition of medicines
- WHO recommendations
- Use of innovations

- Civil society
- Policy makers
- Health personnel
- Supply chain managers
- Drug regulators

Equitable access to good quality, effective and affordable medicines in a sustainable way is a human right.



Greater attention should be given to quality of uterotonics and WHO recommendations. Countries need to invest in human and technical capacity to ensure that quality and safety of medicines are monitored effectively and continuously by government agencies, starting when drugs are manufactured until they are administered to the patients.

Thank you



- **2015:** WHO/UNICEF joint statement “Temperature-sensitive health products in the expanded programme on immunization cold chain” https://www.rhsupplies.org/uploads/tx_rhscpublications/EPI-cold-chain-WHO-UNICEF-joint-statement_A4_rev2_5-14-15-3.pdf
- **2017:** Quality of oxytocin and storage T variations along supply chain in Ghana <https://pubmed.ncbi.nlm.nih.gov/28551064/>
- **2018:** WHO recommendations on uterotonics for PPH prevention – oxytocin good quality https://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548502/en/
- **2019:** PQ notice on oxytocin temperature storage <https://extranet.who.int/pqweb/sites/default/files/documents/150%20stability%20data%20Oxytocin%20Oct2018.pdf>
 WHO/UNICEF/UNFPA joint statement “Appropriate Storage and Management of Oxytocin – a Key Commodity for Maternal Health” World Health Organization. (2019). WHO/UNICEF/UNFPA joint statement: appropriate storage and management of oxytocin – a key commodity for maternal health. World Health Organization. <https://apps.who.int/iris/handle/10665/311524>
- **2020:** Assessment of Shelf Life and Storage Conditions of Registered Oxytocin Products in Southern African Countries. (*to be published*)
- **2021:** Regulatory guidance for assessment and management of oxytocin applications <https://www.who.int/publications/i/item/9789240022133>
- **2022:** PMS survey on oxytocin and misoprostol in Côte d’Ivoire and Senegal (*to be published*)