Heat-Stable Carbetocin for the Prevention of Postpartum Haemorrhage*

*Heat-stable carbetocin is indicated for the prevention of uterine haemorrhage due to postpartum uterine atony.

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Introduction

Postpartum Haemorrhage is preventable

It is a leading cause of maternal mortality in both rich and poor countries

- All pregnant women are at risk of PPH
- Many women who survive PPH suffer severe morbidity

The actual burden is grossly under-estimated

- Feasibility of accurate measurement in routine care difficult
- Existing measurement options have inaccuracies
- Data on PPH is not routinely captures

Uganda

One in three women have anaemia in pregnancy

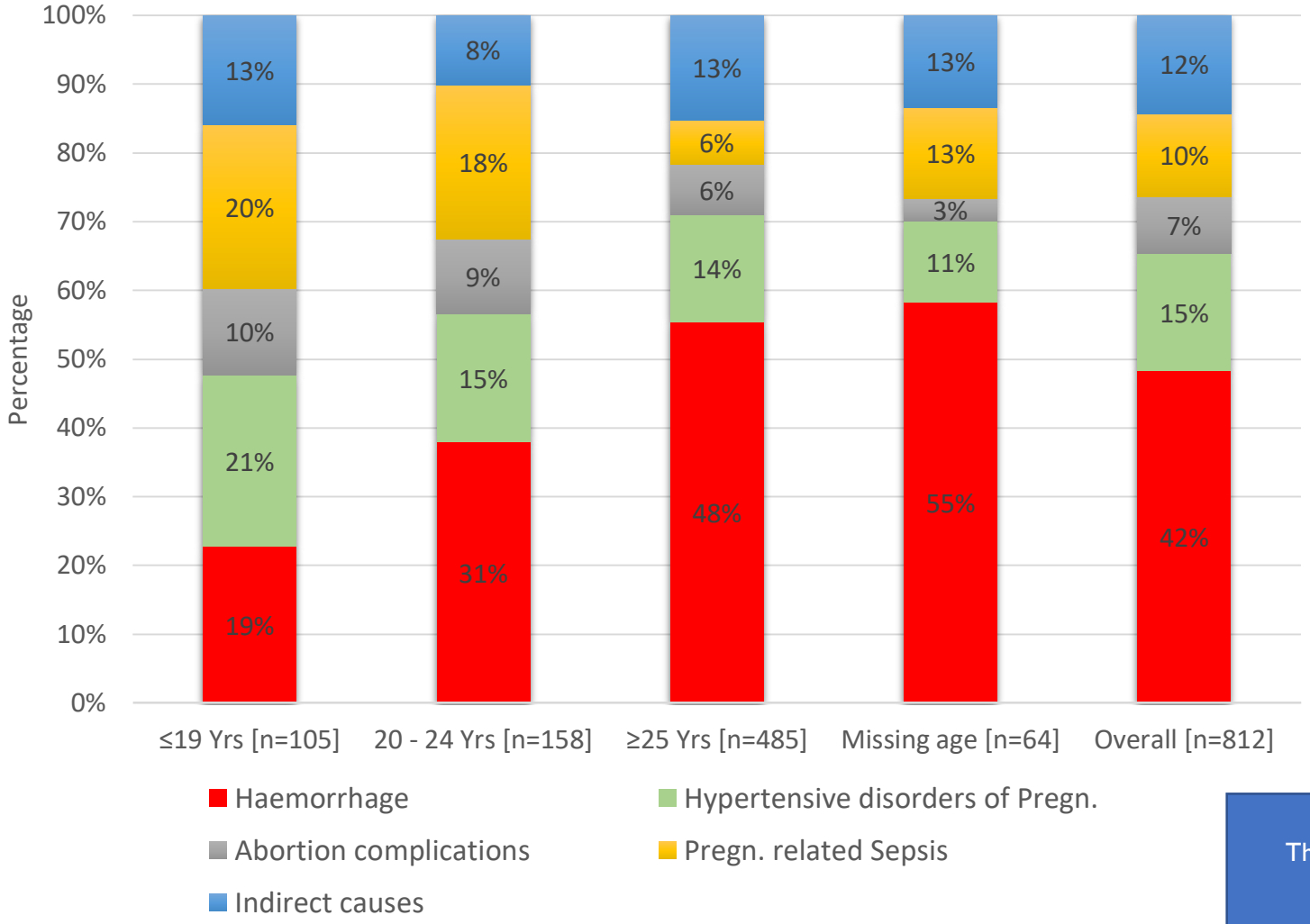
- Risk of PPH when anaemic is 50%

PPH Case fatality 2.3%

PPH is responsible for 34% of all maternal deaths reviewed

THE REPUBLIC OF UGANDA

Five (5) leading causes by maternal age

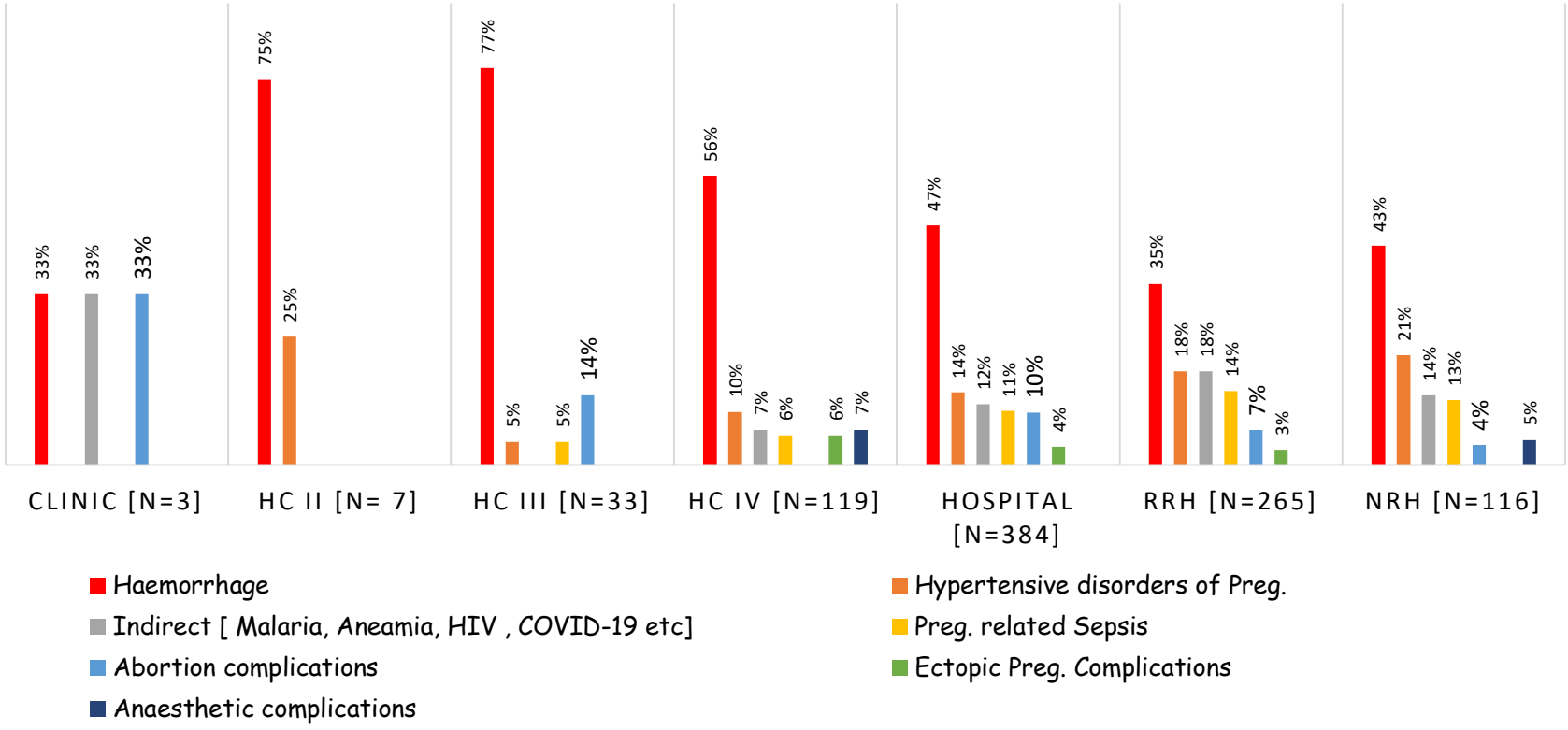


- 42% of facility MDs are obstetric haemorrhage
  - PPH contributed 80%
  - APH contributed 20%
- 15% hypertensive disorders of pregnancy
- 10% are sepsis

The National Annual Maternal and Perinatal Death Surveillance and Response (MPDSR) Report FY 2020/2021

THE REPUBLIC OF UGANDA

Six (6) leading causes of maternal deaths by Health Facility level, FY2020/21



- Haemorrhage was the leading cause of death across all levels of health care with the biggest contribution at health centre II and III levels.
- At HC IV and above, the maternal deaths were due to multiple causes.

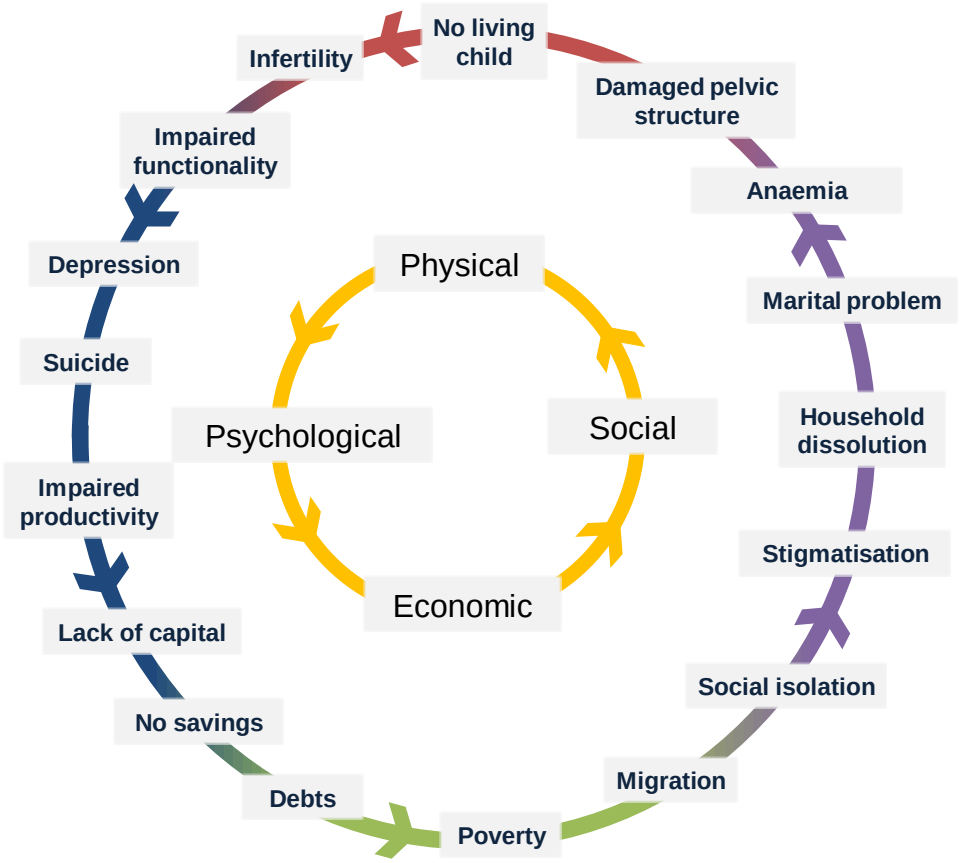
Data source: DHIS2, 2020/21.

Maternal Morbidity

Maternal morbidity due to PPH has a negative impact on women, their families, and communities in LMICs

- Immediate health complications due to PPH include hypovolaemic shock, heart or renal failure, loss of fertility (hysterectomy), and sepsis[1]
- Long-term consequences: when a mother experiences severe morbidities, it results in negative physical, psychological, financial, and social consequences, which can also have a negative impact on her family[2-5]

Consequences of maternal death and near-miss[2,3]

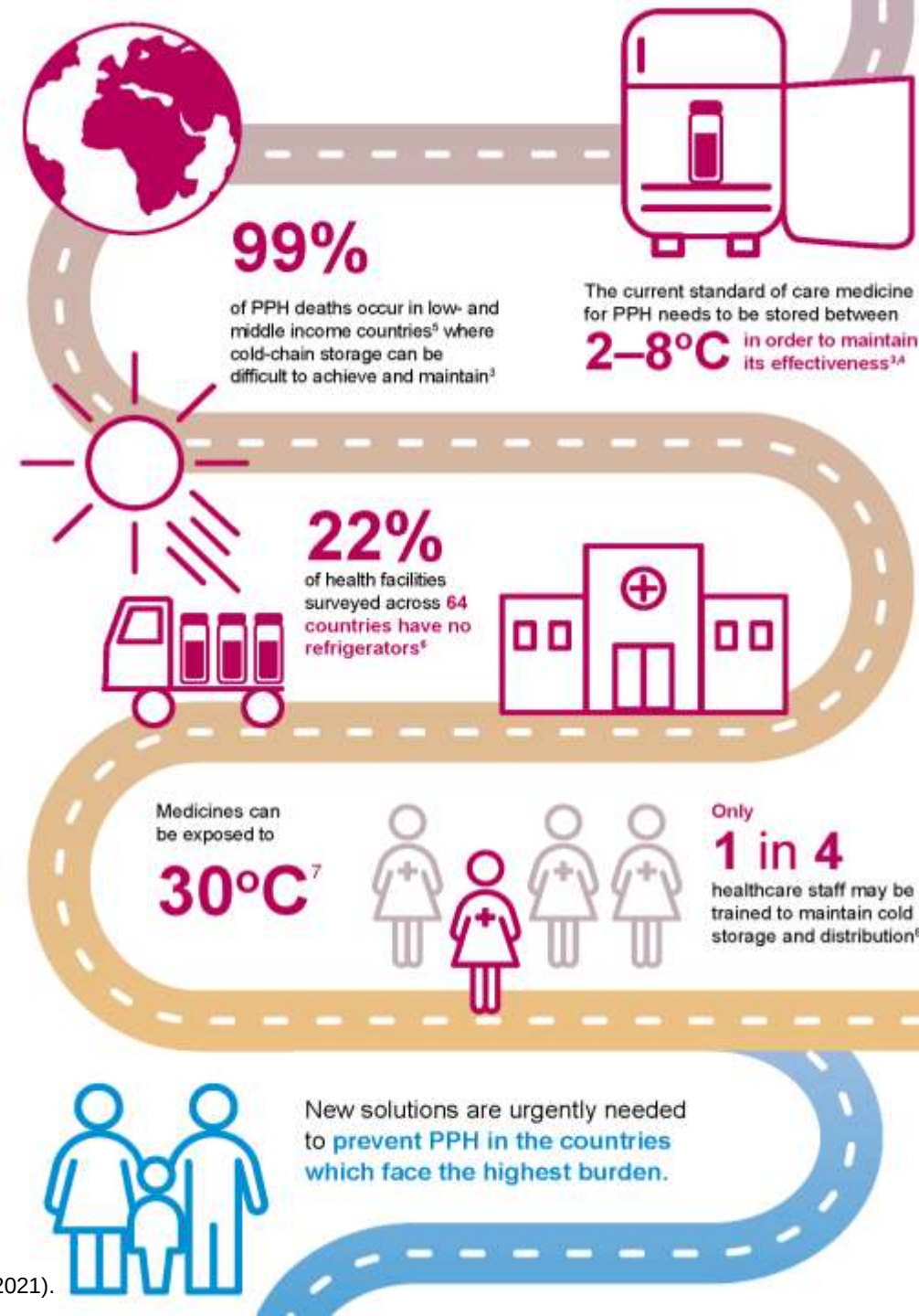


1. Olowokere, A. E., *et al*. (2013). *International Journal of Nursing and Midwifery* 5(3) 28-34.
2. Immpact (2007). *Population Reference Bureau (PRB).*
3. Filippi, V., C, *et al.* (2006). *The Lancet* 368(9546) 1535-1541.
4. Filippi, V., *et al.* (2007). *The Lancet* 370:1329-37.
5. Iyengar, K., *et al.* (2012). *Journal of Health, Population and Nutrition* 30(2):226-240.

Overcoming the Heat Barrier to Prevent PPH

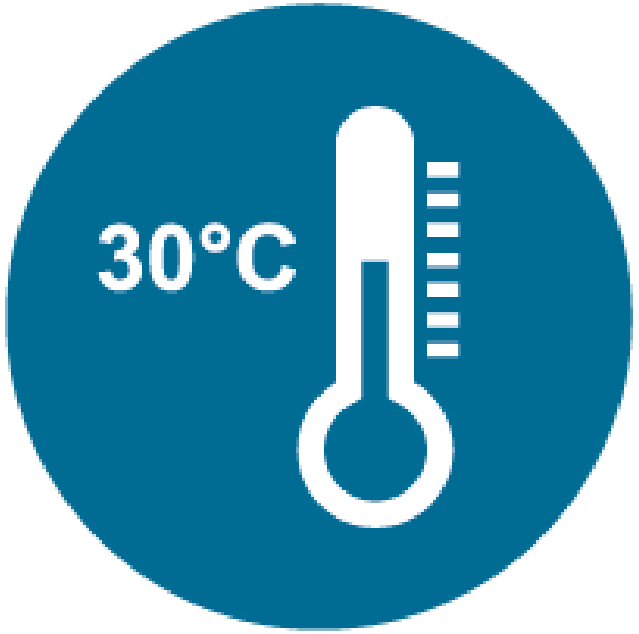
The majority of deaths from PPH due to uterine atony could be prevented[1]

- But oxytocin, the current standard of care uterotonic, requires sustained cold-chain transport and storage at 2–8°C, typically in a refrigerator, to maintain its effectiveness[1,2]
- This poses a challenge in many low- and middle-income countries, where access to sustained cold-chain storage may not be readily available[1]



1. Say L, et al. Lancet Global Health 2014;2:323–333.
2. World Health Organization (2018). Available at apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1&ua=1 (Last accessed: July 2021).
3. Widmer M, et al. Trials 2016;17:143.
4. Torloni MR, et al. BJOG 2016;123:2076–2086.
5. World Health Organization. Available at: www.who.int/medicines/areas/priority_medicines/Ch6_16PPH.pdf (Last accessed: July 2021).
6. World Health Organization. Available at: www.who.int/immunization/programmes_systems/supply_chain/resources/WHO_CTC_Infographic.pdf?ua=1 (Last accessed: July 2021).
7. Kartoglu U, et al. Biologicals 2017; 50:117–124. **8.** Immunization Supply Chain Policy Environment in Uganda. Landscape Analysis and Advocacy Recommendations. Available at: www.path.org/publications/files/APP_landscape_analysis_uganda_rpt.pdf (Last accessed July 2021).

A Heat-Stable Uterotonic



- HSC does not need to be transported or stored at 2-8°C
- HSC is stable for 48 months when stored below 30°C (but not frozen)[1]
- HSC does not require refrigeration, reducing pressure on fragile cold-chain transport and refrigerated storage infrastructure in LMICs[2]

1. Carbetocin Ferring Summary of Product Characteristics https://www.swissmedicinfo.ch/?Lang=EN (Last accessed July 2021).
2. Widmer, M., et al. (2018). New England Journal of Medicine 379, 743-752. Available at: DOI: 10.1056/NEJMoa1805489.

Heat-Stable Carbetocin is Different from Oxytocin

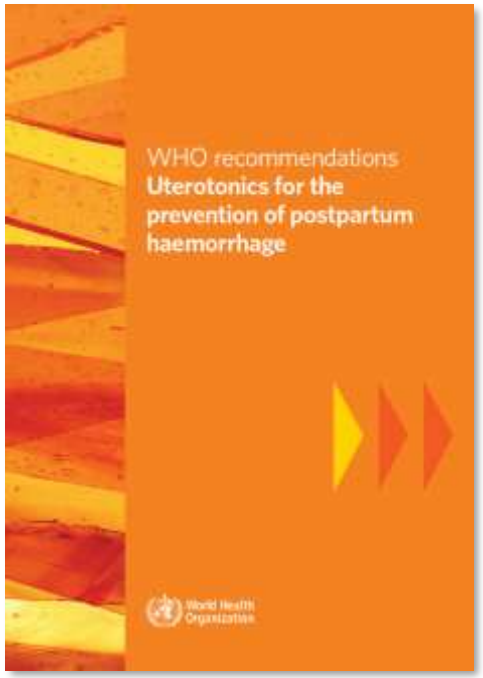
- Carbetocin is a long acting synthetic analogue of oxytocin that contracts the uterus[1]
- The 2018 WHO Recommendations[1] support the use of carbetocin in the prevention of PPH for all births in contexts where its cost is comparable to other effective uterotonics. Carbetocin is recommended in settings where oxytocin is unavailable or its quality cannot be guaranteed
- Carbetocin has been added to the WHO Model List of Essential Medicines[2]
- Heat-stable carbetocin is approved for the prevention of uterine haemorrhage due to postpartum uterine atony following caesarean section & vaginal delivery (under the new Swissmedic and MAGHP* procedure)[3]

*MAGHP: Swiss Marketing Authorization for Global health Products.

1. Widmer, M., et al. (2018). *New England Journal of Medicine* 379, 743-752. Available at: DOI: 10.1056/NEJMoa1805489.
2. World Health Organization Model List of Essential Medicines, 21st List, 2019. Geneva: World Health Organization; 2019.
3. Swissmedic. First MAGHP approval in Switzerland. Available at: www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/information/first-maghp-approval-inswitzerland.html (Last accessed: July 2021).

WHO Recommendations [1/2]

Heat-stable carbetocin is now amongst the uterotonics recommended by WHO for the prevention of PPH



Recommendation 1

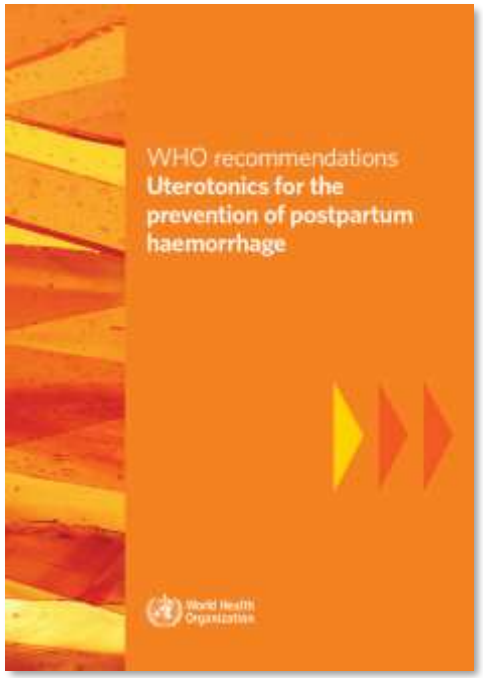
The use of an effective uterotonic for the prevention of PPH during the third stage of labour is recommended for all births.
To effectively prevent PPH, only one of the following uterotonics should be used:[1]

1. Oxytocin
2. Carbetocin*
3. Misoprostol
4. Ergometrine/methylergometrine
5. Oxytocin and ergometrine fixed-dose combination

*Heat-stable carbetocin is indicated for the prevention of uterine haemorrhage due to postpartum uterine atony.

1. World Health Organization. WHO Recommendations. Uterotonics for the Prevention of Postpartum Haemorrhage. 2018.

WHO Recommendations [2/2]



Recommendation 1.1

The use of oxytocin (10 IU, IM/IV) is recommended for the prevention of PPH for all births[1]

Recommendation 1.2

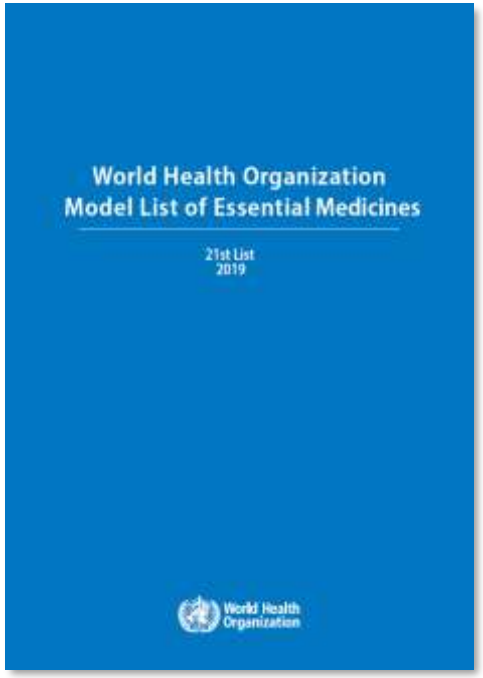
The use of carbetocin (100 mcg, IM/IV) is recommended for the prevention of PPH for all births in contexts where its cost is comparable to other effective uterotonics[1]

Recommendation 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[1]

1. World Health Organization. WHO Recommendations. Uterotonics for the Prevention of Postpartum Haemorrhage. 2018.

HSC is Included in the WHO Essential Medicines List



22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE

22.3 Uterotonics	
carbetocin	**Injection (heat stable):** 100 micrograms/mL
☐ ergometrine	**Injection:** 200 micrograms (hydrogen maleate) in 1- mL ampoule.
mifepristone – misoprostol Where permitted under national law and where culturally acceptable.	**Tablet** 200 mg – **tablet** 200 micrograms. **Co-package containing:** mifepristone 200 mg tablet [1] and misoprostol 200 microgram tablet [4]
misoprostol	**Tablet:** 200 micrograms. – Management of incomplete abortion and miscarriage; – Prevention and treatment of postpartum haemorrhage where oxytocin is not available or cannot be safely used **Vaginal tablet:** 25 micrograms.* * Only for use for induction of labour where appropriate facilities are available.
oxytocin	**Injection:** 10 IU in 1- mL.

1. World Health Organization model list of essential medicines: 21st list 2019.

Uterotonic Agents Used in the Prevention of PPH

Class of drug	Example	Mechanism of action
Oxytocin	Oxytocin	• Binds at oxytocin receptors and stimulates myometrial smooth muscle contractions[1]
Long-acting oxytocin analogue	Carbetocin	• Same as oxytocin, but duration of uterine activity is longer[2]
Ergot alkaloids	Ergometrine*	• Significantly increase smooth muscle activity[2] • Produces myometrial contractions via calcium channel mechanism and actin–myosin interaction[2]
Ergot alkaloids and oxytocin	Syntometrine* (500 mcg ergometrine + 5 IU oxytocin)	• Same as ergometrine (sustained myometrial contractions) and oxytocin (rapid onset of action)[3]
Prostaglandins	Misoprostol	• Involved in cervical ripening[4] • Increases myometrial contractions via cervical smooth muscle relaxation and increasing intracellular calcium[2]

*Contraindicated in cases of severe hypertension, pre-eclampsia, and eclampsia[3,5]

1. Arrowsmith S, Wray S. J Neuroendocrinol 2014;26:356–369.
2. Prendiville W, O'Connell M. Management and Surgical Intervention 2006;98–113.
3. Alliance Pharmaceuticals. Syntometrine Summary of Product Characteristics. 2019.
4. Kelly RW. J Reprod Immunol 2002;57:217–224.
5. Hameln Pharma Ltd. Ergometrine Injection Summary of Product Characteristics. 2018.

Clinical Value of Heat-Stable Carbetocin

- HSC does not require refrigeration and can be stored for up to 48 months (at 30°C)
- HSC is given as a single dose, and easy to administer for the prevention of PPH*
- **According to a network meta-analysis conducted in 2018 by Gallos, *et al*:**
  - Heat-stable carbetocin (HSC) is the highest-ranked single uterotonic agent for the prevention of blood loss ≥ 500mL[1]
  - HSC may also reduce the use of additional uterotonics[1]
  - HSC and oxytocin have the most favourable side effect profiles among uterotonics to prevent PPH[1*]

*Heat-stable carbetocin is indicated for the prevention of uterine haemorrhage due to postpartum uterine atony.

1. Gallos, et al. (2018). Cochrane Database Syst Rev (4): CD011689.

HSC has a Favourable Safety Profile[1]

Per the meta-analysis, heat-stable carbetocin and oxytocin have the most favourable side effect profiles among uterotonics to prevent PPH*

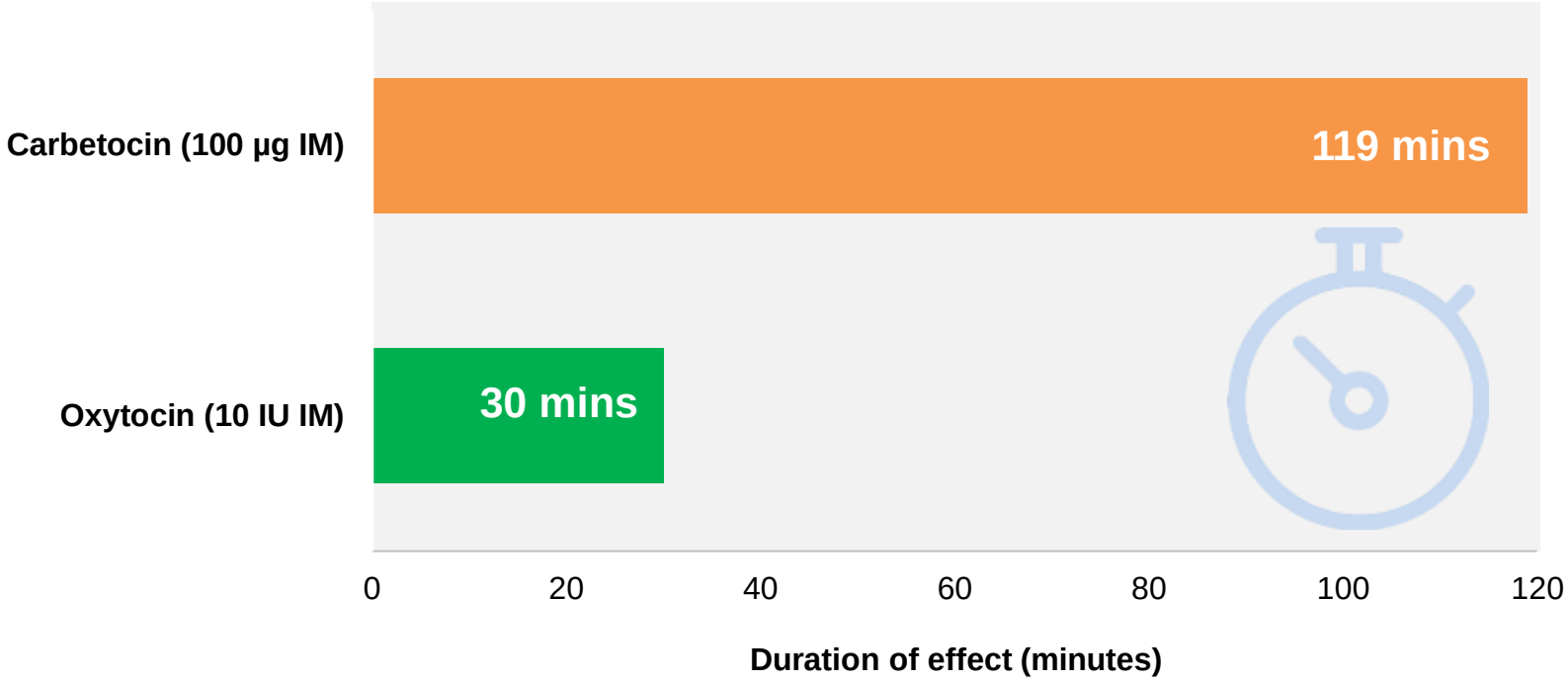
- Heat-stable carbetocin and oxytocin have a comparable safety profile
- Heat-stable carbetocin is the only uterotonic comparable to oxytocin across all side effects assessed in the network meta-analysis[1] including fever, nausea, shivering and vomiting

*Heat-stable carbetocin is indicated for the prevention of uterine haemorrhage due to postpartum uterine atony.

1. Gallos, et al. (2018). Cochrane Database Syst Rev (4): CD011689.

Heat-stable carbetocin is long acting and effective for the prevention of PPH*

Duration of effect for IM injection of heat-stable carbetocin and oxytocin[39,44†]



*Heat-stable carbetocin is indicated for the prevention of uterine haemorrhage due to postpartum uterine atony; †Based on a single IM dose.
IM, intramuscular; IU, international unit; PPH, postpartum haemorrhage.

Heat-Stable Carbetocin Indication

Heat-stable carbetocin is approved for the prevention of uterine haemorrhage due to postpartum uterine atony[1*]

- Heat-stable carbetocin must be administered only after the delivery of the infant[1,2]

*Heat-stable carbetocin is not approved for use in all jurisdictions. Registration to some LMICs still ongoing.

1. Carbetocin Ferring Summary of Product Characteristics https://www.swissmedicinfo.ch/?Lang=EN (Last accessed July 2021).
2. Leathersich SJ, et al. Cochrane Database Syst rev 2018;7:CD009770.

HSC – Contraindications[1]

Heat-stable carbetocin must NOT be used:

- For labour induction or labour augmentation
- During pregnancy and labour before the childbirth
- In women with serious cardiovascular disorders
- In women with hepatic or renal disorders
- In women with epilepsy
- In women with hypersensitivity to carbetocin, oxytocin or any of the excipients according to the composition

1. Carbetocin Ferring Summary of Product Characteristics https://www.swissmedicinfo.ch/?Lang=EN (Last accessed July 2021).

Heat-stable carbetocin warnings[1]

- **The use of heat-stable carbetocin at any stage before delivery of the infant is not appropriate because its uterotonic activity persists for several hours**
- Rule out the presence of another baby (multiple gestation) before administration
- **Heat-stable carbetocin is contraindicated during pregnancy, including for the induction of labour**

Never inject heat-stable carbetocin before the birth of the infant!

1. Carbetocin Ferring Summary of Product Characteristics https://www.swissmedicinfo.ch/?Lang=EN (Last accessed July 2021).

HSC – Composition and Packaging

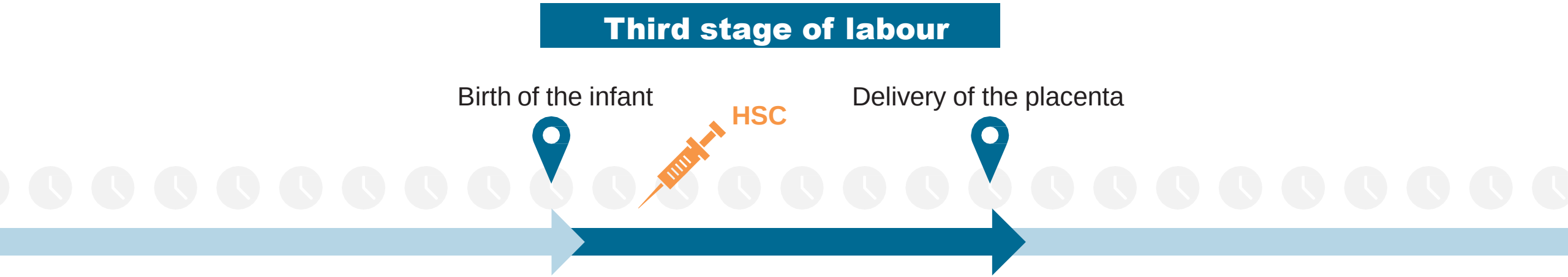
Carbetocin Ferring™ (HSC)

- Commercial packs contain 10 ampoules per box (sufficient for 10 patients)
- The pack has an orange background to differentiate with other uterotonic drugs
- Ampoules of 1 ml, each containing 100 micrograms of carbetocin[1]
- In addition to carbetocin, the solution contains water; L-Methionine; Succinic acid; Mannitol and Sodium hydroxide[1]

1. Carbetocin Ferring Summary of Product Characteristics https://www.swissmedicinfo.ch/?Lang=EN (Last accessed July 2021).

HSC – Administration[1] [1/4]

Heat-stable carbetocin must be injected as soon as possible after the birth of the infant and preferably before delivery of the placenta



HSC should only be administered by skilled health personnel.

Make sure this is not a multiple gestation.
If another baby is present, do not inject HSC.
Inject HSC after all of the babies are born.

1. Carbetocin Ferring Summary of Product Characteristics https://www.swissmedicinfo.ch/?Lang=EN (Last accessed July 2021).

HSC – Administration[1] [2/4]

1 ampoule, not diluted

The solution in the ampoule is for use undiluted for intravenous IV and intramuscular IM injection

Use a 2ml syringe for injection

The ampoule solution should NOT be diluted before injection

One ampoule of 1ml (100 micrograms) is the dose for one patient

Administering more than one dose is not recommended as it has not been studied

*Heat-stable carbetocin is indicated for the prevention of uterine haemorrhage due to postpartum uterine atony.
IV: intravascular ; IM: intramuscular

1. Carbetocin Ferring Summary of Product Characteristics https://www.swissmedicinfo.ch/?Lang=EN (Last accessed July 2021).

HSC – Administration[1] [3/4]

For IV injection

Heat-stable carbetocin can be administered in both vaginal birth and caesarean section.

1 ml (100 micrograms) administered slowly over 1 minute directly in the IV port.

Do not inject HSC into the intravascular fluid bag

Inject over 1 min

IV: intravascular.

1. Carbetocin Ferring Summary of Product Characteristics https://www.swissmedicinfo.ch/?Lang=EN (Last accessed July 2021).

HSC – Administration[1] [4/4]

For IM injection

1 ml (100 micrograms) can also be administered intramuscularly.

IM: intramuscular.

1. Carbetocin Ferring Summary of Product Characteristics https://www.swissmedicinfo.ch/?Lang=EN (Last accessed July 2021).

Heat-Stable Carbetocin Interactions[1]

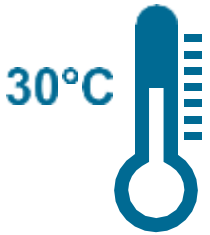
- Heat-stable carbetocin can be administered for prevention of PPH* even if oxytocin or other uterotonics have been given during labour
- If bleeding occurs after administration of heat-stable carbetocin for the prevention of PPH*, follow local protocols
- Tranexamic acid and/or uterotonics can be administered according to local standards

No interaction studies have been undertaken with carbetocin. During clinical trials, Carbetocin Ferring has been administered in association with analgesics, antibiotics, antiretrovirals, spasmolytics and agents used for epidural or spinal anaesthesia. No drug interactions were observed.

*Heat-stable carbetocin is indicated for the prevention of uterine haemorrhage due to postpartum uterine atony.

1. Carbetocin Ferring Summary of Product Characteristics https://www.swissmedicinfo.ch/?Lang=EN (Last accessed July 2021).

HSC – Storage[1]



Heat-stable carbetocin remains stable for 48 months if stored below 30°C and 75% relative humidity (approved storage conditions).

Data is available supporting higher temperature deviations during transport.[2]

Do not freeze

Ampoules must be kept in the outer carton to protect the product from light during storage

It must be used before the expiry date marked “Exp.” on the pack

1. Carbetocin Ferring Summary of Product Characteristics https://www.swissmedicinfo.ch/?Lang=EN (Last accessed July 2021). **2.** Malm M, et al. J Pept Sci. 2018;24(6):e3082.

Uganda's Progress

1. Approval from MOH : (MCH TWG, PM TWG, Senior management, Top management)
2. NDA Registration
3. Included in Essential Maternal and Newborn Care guidelines

Plans

1. Inclusion in Essential Medicines & health supplies list of UG
2. UCG
3. Procurement of URMCHIP
4. Training on correct use

Heat-Stable Carbetocin in Summary

- Is a **WHO-recommended uterotonic** for the prevention of PPH* and is on WHO's Essential Medicines List (EML)[1]
- Has a **longer duration** of uterine activity than oxytocin[2]
- Is **beneficial for use in PPH prevention***, but HSC should not be used during pregnancy or before birth of the baby[3,4]
- Heat-stable carbetocin and oxytocin have the **most favourable side effect profiles** among uterotonics to prevent PPH[5*]
- **Is the only injectable uterotonic that can be stored in the approved storage condition at 30°C for 48 months[4]**
- **Only 1 dose** (1 ml ampoule of 100 micrograms) injected IM or IV – for vaginal delivery and caesarean section[4]

*Heat-stable carbetocin is indicated for the prevention of uterine haemorrhage due to postpartum uterine atony.

1. World Health Organization. Model List of Essential Medicines, 21st List, 2019. Available at: https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf (Last accessed September 2021).
2. Prendiville W, O'Connell M. Management and Surgical Intervention 2006;98–113.
3. World Health Organization. WHO Recommendations. Uterotonics for the Prevention of Postpartum Haemorrhage. 2018.
4. Carbetocin Ferring Summary of Product Characteristics https://www.swissmedicinfo.ch/?Lang=EN (Last accessed July 2021).
5. Gallos, et al. (2018). Cochrane Database Syst Rev (4): CD011689.