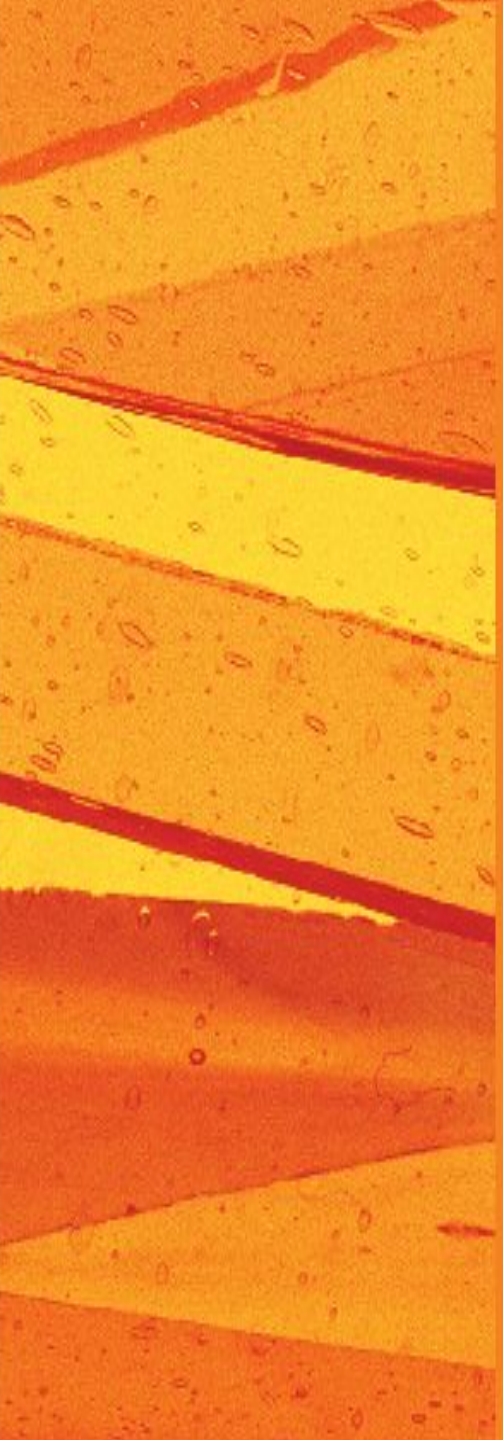


WHO recommendations Uterotonics for the prevention of postpartum haemorrhage

World Health Organization

table of contents

1. the global burden of postpartum haemorrhage

What is postpartum haemorrhage?

Postpartum haemorrhage (PPH) is the leading cause of maternal death worldwide.

Postpartum haemorrhage (PPH) is commonly defined as a blood loss of 500 ml or more within 24 hours after birth. It affects about 5% of all women giving birth around the world.

Globally, nearly one quarter of all maternal deaths are associated with PPH. In most low-income countries, it is the main cause of maternal mortality.

The majority of PPH-associated deaths could be avoided by the use of prophylactic uterotonics during the third stage of labour and appropriate treatment.

Improving health care for women during childbirth to prevent and treat PPH is a necessary step towards achievement of the health targets of the Sustainable Development Goals (SDGs).

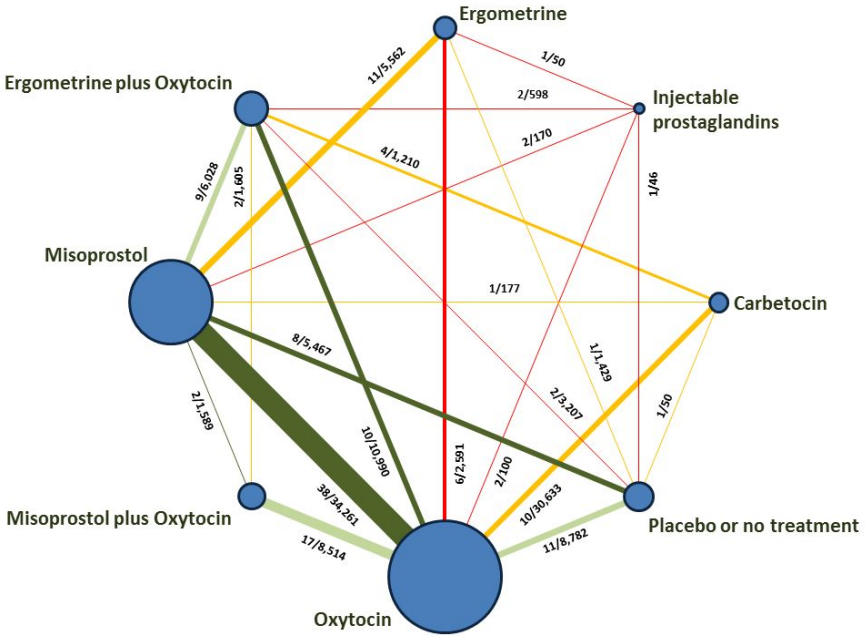
99% of all maternal deaths occur in low- and middle-income countries (LMICs).

2. Uterotonics for PPH prevention

New findings on uterotonics for PPH prevention

A Cochrane systematic review and network meta-analysis compared uterotonic options with no uterotonic and other uterotonic options.

- 196 trials (135 559 women) across 53 countries
- Any trial comparing a uterotonic vs placebo, no uterotonic or another uterotonic
- Single agents (oxytocin, carbetocin, misoprostol, ergometrine) or combination agents (oxytocin plus ergometrine, oxytocin plus misoprostol)



Gallos et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev. CD011689.

2. Uterotonics for PPH prevention

New findings on uterotonics for PPH prevention

A Cochrane systematic review and network meta-analysis compared all uterotonic options and placebo or no treatment.

- 196 trials (135 559 women) across 53 countries
- Any trial comparing a uterotonic vs placebo, no treatment or another uterotonic
- Single agents (oxytocin, carbetocin, misoprostol, ergometrine) or combination agents (oxytocin plus ergometrine, oxytocin plus misoprostol)

In light of this new evidence, the WHO recommendations on uterotonics for PPH prevention have been updated

The WHO PPH recommendations were first published in 2012.

These updated recommendations (2018) supersede the previous recommendations on uterotonics for PPH prevention.

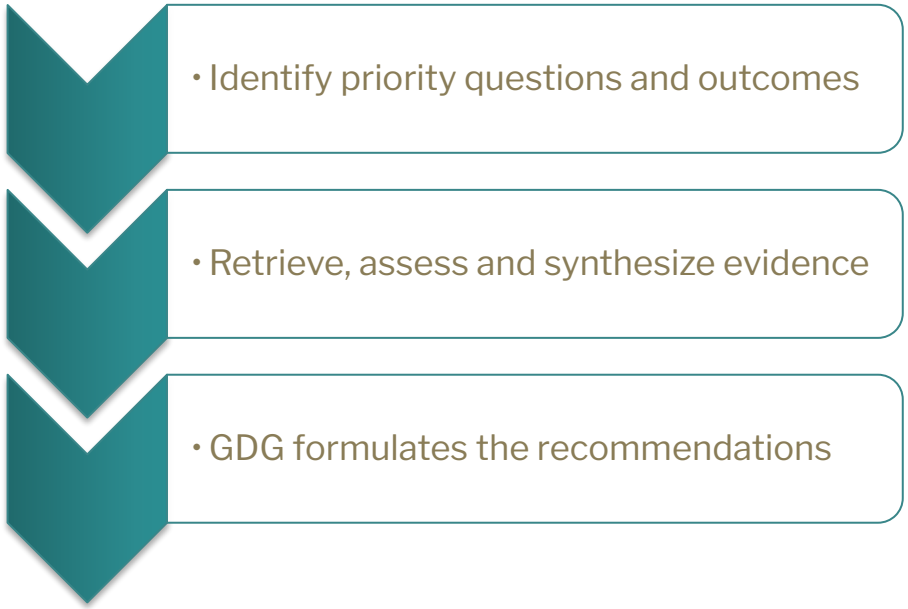
3. how were the WHO recommendations updated?

A systematic approach

The recommendations were updated according to the standards of the WHO handbook on guideline development

Updating involves:

1. WHO Steering Group
2. Guideline Development Group (GDG)
3. Executive Guideline Steering Group (GSG)
4. External Review Group
5. Systematic review team
6. External partners and observers



3. how were the WHO recommendations updated?

GDG formulates the recommendations

The Guideline Development Group (GDG) convened in September & October 2018

The GDG comprised 18 external experts and relevant stakeholders with expertise in research, guideline development, policy and programmes on PPH prevention and treatment.

GDG members considered:

- Balance between desirable and undesirable effects
- Overall quality of supporting evidence
- Values and preferences of stakeholders
- Resource requirements
- Cost-effectiveness
- Acceptability
- Feasibility
- Equity

4. What are the updated WHO recommendations?

What works?

Efficacy and safety of uterotonics for PPH prevention

uterotonic options
vs
placebo or no treatment

Which one?

Choice of uterotonics for PPH prevention

uterotonic options
vs
other uterotonic options

4. What works: efficacy and safety of uterotonics for PPH prevention

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:

- Oxytocin
- Carbetocin
- Misoprostol
- Ergometrine/methylergometrine
- Oxytocin and ergometrine fixed-dose combination

4. What works: efficacy and safety of uterotonics for PPH prevention

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:

- **Oxytocin**
- Carbetocin
- Misoprostol
- Ergometrine/methylergometrine
- Oxytocin and ergometrine fixed-dose combination

Recommendation 1.1

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

- Vaginal birth or caesarean section
- Skilled health personnel required to administer
- At caesarean section: consider dividing doses and avoid a rapid IV bolus

4. What works: efficacy and safety of uterotonics for PPH prevention

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:

- Oxytocin
- **Carbetocin**
- Misoprostol
- Ergometrine/methylergometrine
- Oxytocin and ergometrine fixed-dose combination

Recommendation 1.2

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

- Vaginal birth or caesarean section
- Skilled health personnel required to administer
- For PPH prevention **only**

4. What works: efficacy and safety of uterotonics for PPH prevention

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:

- Oxytocin
- Carbetocin
- **Misoprostol**
- Ergometrine/methylergometrine
- Oxytocin and ergometrine fixed-dose combination

Recommendation 1.3

The use of misoprostol (either 400 µg or 600 µg PO) is recommended for the prevention of PPH for all births.

- Alternative routes may be needed at caesarean section, but oral route is preferred by women
- No clear evidence of which dose is superior, but higher doses have more side effects
- Inform women of possible adverse effects
- Can be used in hospital or community

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:

- Oxytocin
- Carbetocin
- Misoprostol
- **Ergometrine/methylergometrine**
- Oxytocin and ergometrine fixed-dose combination

Recommendation 1.4

The use of ergometrine (200 µg, IM/IV) is recommended for the prevention of PPH in contexts where hypertensive disorders can be safely excluded prior to its use

- Vaginal birth or caesarean section
- Skilled health personnel are required
- Inform women of possible side effects - other options may have better side effect profile

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:

- Oxytocin
- Carbetocin
- Misoprostol
- Ergometrine/methylergometrine
- **Oxytocin and ergometrine fixed-dose combination**

Recommendation 1.5

The use of oxytocin and ergometrine fixed-dose combination (5 IU/500 µg IM) is recommended for the prevention of PPH in contexts where hypertensive disorders can be safely excluded prior to its use.

- Vaginal birth or caesarean section
- Skilled health personnel are required

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:

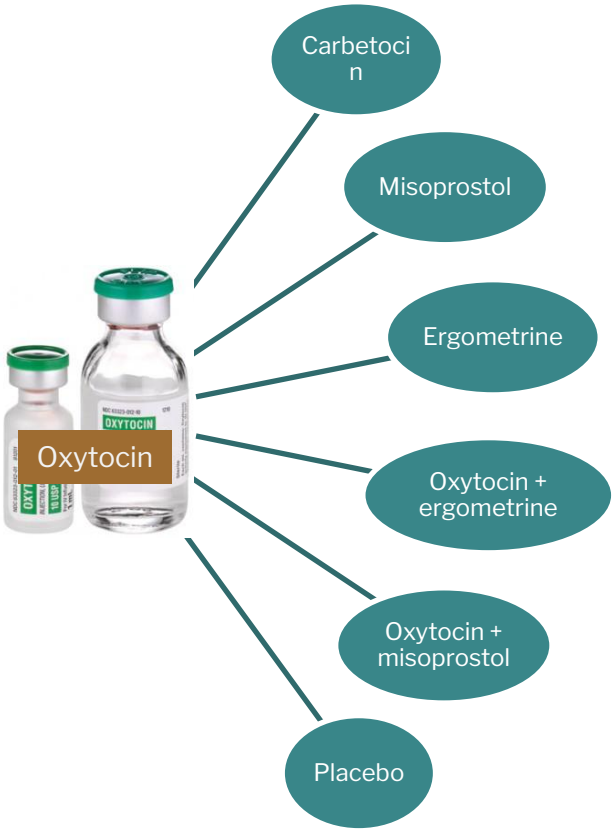
- Oxytocin
- Carbetocin
- Misoprostol
- Ergometrine/methylergometrine
- Oxytocin and ergometrine fixed-dose combination

- **Injectable prostaglandins**

Recommendation 1.6

Injectable prostaglandins (carboprost or sulprostone) are not recommended for the prevention of PPH

How do we compare uterotonics to one another?

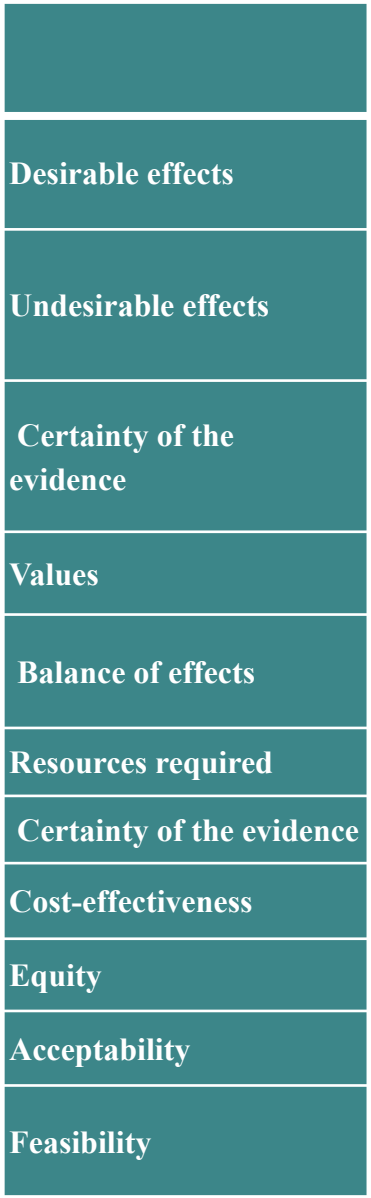


Comparing uterotonics through **oxytocin** as a common comparator

- Oxytocin is current standard of care
- Largest number of trials in the network meta-analysis
- The natural sequence for introducing a new uterotonic option is to evaluate efficacy with the “gold standard” option

Desirable outcomes	Oxytocin (absolute risk)	Carbetocin	Misoprostol	Injectable prosta-glandins	Ergometrine	Oxytocin plus ergometrine	Misoprostol plus oxytocin
Maternal death							
PPH ≥ 1000 ml							
Blood transfusion							
ICU admissions							
PPH ≥ 500 ml							
Additional uterotonics							
Blood loss							
Change in haemoglobin							
Breastfeeding							

4. Which one: Summary of judgements comparing uterotonics to oxytocin (reference)



These criteria were considered by the GDG for each uterotonic option

4. Which one: Summary of judgements comparing uterotonics to oxytocin (reference)

Uterotonic options:	Oxytocin
Desirable effects	Reference
Undesirable effects	Reference
Certainty of the evidence	Reference
Values	Probably no important uncertainty or variability
Balance of effects	Reference
Resources required	Reference
Certainty of the evidence	Reference
Cost-effectiveness	Reference
Equity	Probably increased
Acceptability	Varies
Feasibility	Probably Yes

Oxytocin is the reference comparator

4. Which one: Summary of judgements comparing uterotonics to oxytocin (reference)

Uterotonic options:	Oxytocin	Carbetocin
Desirable effects	Reference	Small
Undesirable effects	Reference	None
Certainty of the evidence	Reference	Moderate
Values	Probably no important uncertainty or variability	Probably no important uncertainty or variability
Balance of effects	Reference	Probably favours carbetocin
Resources required	Reference	Moderate costs
Certainty of the evidence	Reference	Low
Cost-effectiveness	Reference	Probably favours oxytocin
Equity	Probably increased	Varies
Acceptability	Varies	Varies
Feasibility	Probably Yes	Probably Yes

Carbetocin compared to oxytocin

- Similar desirable effects, and carbetocin likely superior in reducing PPH (≥ 500 ml) (41 fewer events per 1000 women), use of additional uterotonics (74 fewer per 1000) and blood loss after birth (81 ml less on average).
- No clear difference in undesirable effects
- While balance of effects probably favours carbetocin, the supply cost of carbetocin is approximately 20 times more than oxytocin
- Uncertain whether the additional benefits justify the additional cost of routinely implementing carbetocin at the current unit price
- Acceptability among stakeholders and impact on health equity would vary across settings compared with oxytocin.

4. Which one: Summary of judgements comparing uterotonics to oxytocin (reference)

Uterotonic options:	Oxytocin	Misoprostol
Desirable effects	Reference	None
Undesirable effects	Reference	Moderate
Certainty of the evidence	Reference	Moderate
Values	Probably no important uncertainty or variability	Probably no important uncertainty or variability
Balance of effects	Reference	Favours oxytocin
Resources required	Reference	Varies
Certainty of the evidence	Reference	Low
Cost-effectiveness	Reference	Varies
Equity	Probably increased	Probably increased
Acceptability	Varies	Probably Yes
Feasibility	Probably Yes	Probably Yes

Misoprostol compared to oxytocin

- Misoprostol has similar desirable effects to oxytocin, but it is less effective for reducing severe PPH (≥ 1000 ml) (7 more events per 1000 women).
- Causes more undesirable effects (including nausea, vomiting, shivering, fever and diarrhoea).
- Misoprostol is cheaper, heat-stable, can be used orally, and is probably acceptable and feasible to use.
- Lower effectiveness for severe PPH and greater undesirable effects may increase costs (these costs may vary according to the setting).
- Can be task-shifted to lay health workers and community health workers.

4. Which one: Summary of judgements comparing uterotonics to oxytocin (reference)

Uterotonic options:	Oxytocin	Ergometrine
Desirable effects	Reference	None
Undesirable effects	Reference	Moderate
Certainty of the evidence	Reference	Low
Values	Probably no important uncertainty or variability	Probably no important uncertainty or variability
Balance of effects	Reference	Probably favours oxytocin
Resources required	Reference	Moderate costs
Certainty of the evidence	Reference	Low
Cost-effectiveness	Reference	Favours oxytocin
Equity	Probably increased	Probably reduced
Acceptability	Varies	Probably Yes
Feasibility	Probably Yes	Probably Yes

Ergometrine / methylergometrine compared to oxytocin

- No clear evidence of difference in desirable effects.
- However, women are more likely to experience nausea, vomiting, headache, hypertension and diarrhoea with ergometrine.
- Costs associated with managing undesirable effects, as well as the need to screen for high blood pressure, implies that oxytocin is probably more cost-effective.
- Ergometrine may have negative effects on health equity in settings with high rates of – or lack of screening for – hypertensive disorders.

4. Which one: Summary of judgements comparing uterotonics to oxytocin (reference)

Uterotonic options:	Oxytocin	Oxytocin plus ergometrine
Desirable effects	Reference	Small
Undesirable effects	Reference	Moderate
Certainty of the evidence	Reference	Moderate
Values	Probably no important uncertainty or variability	Probably no important uncertainty or variability
Balance of effects	Reference	Favours oxytocin
Resources required	Reference	Negligible costs or savings
Certainty of the evidence	Reference	Low
Cost-effectiveness	Reference	Probably favours oxytocin
Equity	Probably increased	Probably reduced
Acceptability	Varies	Probably Yes
Feasibility	Probably Yes	Varies

Oxytocin plus ergometrine compared to oxytocin

- Similar to oxytocin in terms of desirable outcomes, though it is possibly more effective in preventing PPH (≥ 500 ml) (44 fewer events per 1000 women).
- More undesirable effects than oxytocin, including nausea, vomiting and diarrhoea.
- Balance of effects clearly favours oxytocin.
- Costs related to undesirable effects, as well as the need to screen for women with hypertensive disorders, imply that oxytocin is probably more cost-effective.
- May have a negative impact on health equity, particularly in settings with limited capacity and capability to routinely screening for hypertensive disorders of pregnancy.

4. Which one: Summary of judgements comparing uterotonics to oxytocin (reference)

Uterotonic options:	Oxytocin	Misoprostol plus oxytocin
Desirable effects	Reference	Moderate
Undesirable effects	Reference	Large
Certainty of the evidence	Reference	Moderate
Values	Probably no important uncertainty or variability	Probably no important uncertainty or variability
Balance of effects	Reference	Favours oxytocin
Resources required	Reference	Varies
Certainty of the evidence	Reference	Low
Cost-effectiveness	Reference	Varies
Equity	Probably increased	Probably increased
Acceptability	Varies	Probably Yes
Feasibility	Probably Yes	Probably No

Misoprostol plus oxytocin compared to oxytocin

- Probably superior to oxytocin for blood transfusion (11 fewer events per 1000 women), additional uterotonic use (58 fewer per 1000) and blood loss (88 ml less on average). May possibly prevent more PPH (≥ 500 ml) (44 fewer per 1000) and result in a smaller mean change in haemoglobin level (before versus after birth).
- Associated with more undesirable effects including nausea, vomiting, diarrhoea, shivering and fever.
- Balance of effects favours oxytocin.
- Cost-effectiveness may vary in different settings.
- Feasibility is limited due to the complexity of using two separate medications through different routes of administration.

4. Which one: Choice of uterotonics for PPH prevention

Recommendation 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.

Vaginal birth or caesarean section

Skilled health personnel are required

Combination of misoprostol and oxytocin may be more effective than oxytocin alone for some priority outcomes, however:

- increases side effects
- not available as a fixed dose combination
- requires parenteral and oral administration

4. Which one: Choice of uterotonics for PPH prevention

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.

Vaginal birth or caesarean section

Skilled health personnel are required

4. Which one: Choice of uterotonics for PPH prevention

Recommendation 4. In settings where skilled health personnel are not present to administer injectable uterotonics, the administration of misoprostol (either 400 µg or 600 µg PO) by community health care workers and lay health workers is recommended for the prevention of PPH.

If skilled health personnel are not present or have not been trained to administer injectable uterotonics, **oral misoprostol** is preferred

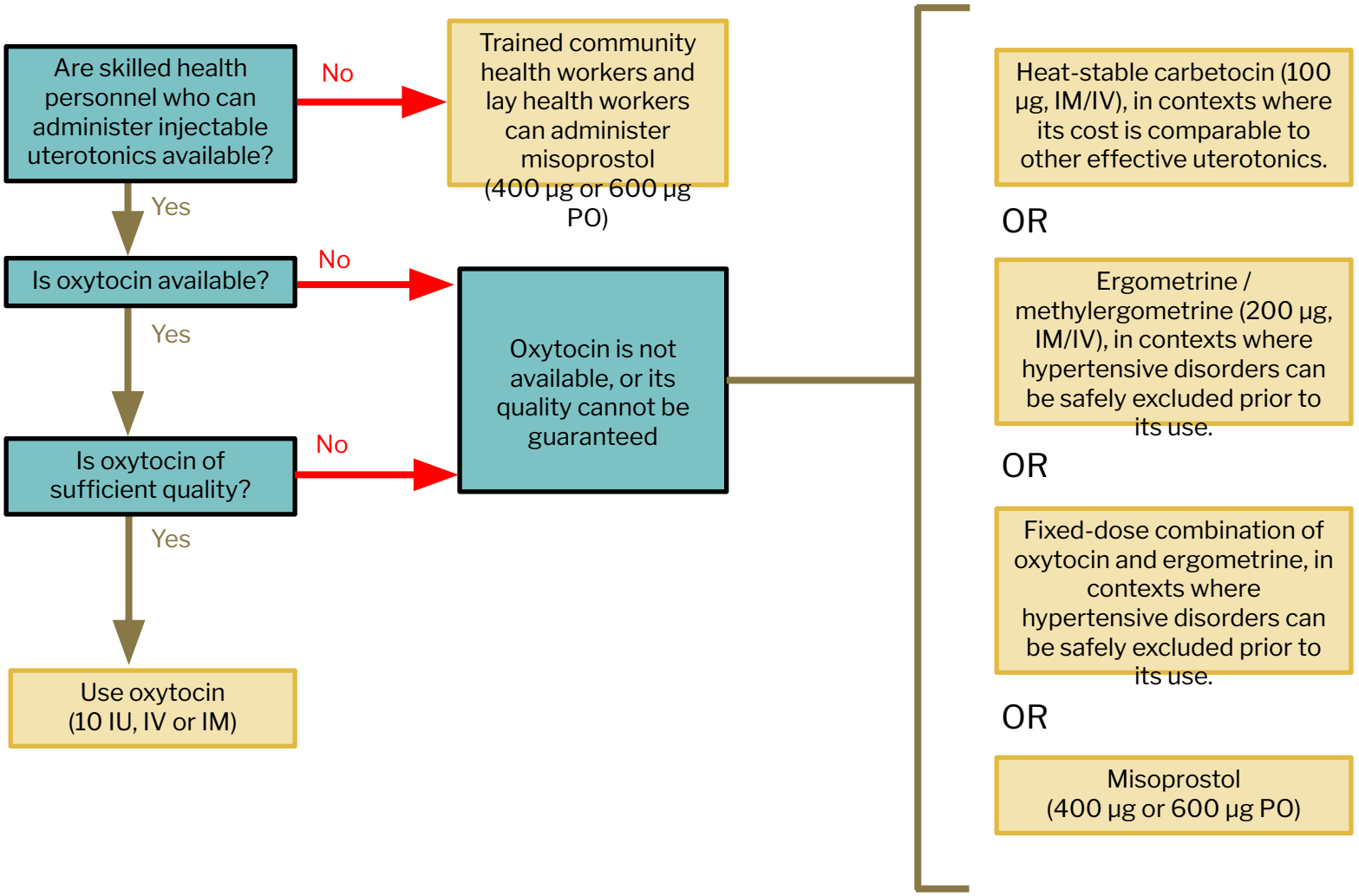
5. What's new: wider scope, more evidence

	2012 recommendations	2018 recommendations
Uterotonics considered		
Evidence base		

5. So what's new: More recommendations, greater specificity

* Context specific recommendation

6. implementing the updated WHO recommendations



Implementation considerations

Update clinical guidance

Develop or revise existing clinical guidelines, protocols or job aids

Equip health facilities

Ensure necessary supplies, equipment and staff to use uterotonics safely

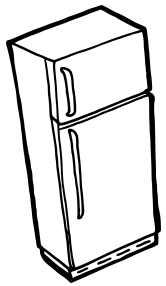
Support behaviour change

Obtain technical support for implementation, engage stakeholders and partners, and provide training

Implementation considerations

Quality-certified uterotonics

Regulatory, procurement and logistics processes that work



Cold-chain transport & storage

For heat-sensitive uterotonics (oxytocin, ergometrine)

Effective communication

Ensure women are informed of risks, benefits and alternatives

Contact us

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