



Quality of oxytocin available in low- and middle-income countries: a systematic review of the literature

MR Torloni,^a C Gomes Freitas,^a UH Kartoglu,^b A Metin Gülmezoglu,^c M Widmer^c

^a Evidence Based Healthcare Post-Graduate Programme, Department of Internal Medicine, São Paulo Federal University, São Paulo, Brazil

^b Department of Essential Medicines and Health Products, World Health Organization, Geneva, Switzerland ^c Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland

Correspondence: Dr MR Torloni, Centro de Ensino e Pesquisa em Avaliações Tecnológicas – CEPATIS, Rua Botucatu, 740 – 3o andar, São Paulo CEP 04023-900, Brazil. Email torlonimr@gmail.com

Accepted 10 February 2016. Published Online 22 March 2016.

Background Oxytocin is the drug of choice for preventing and treating postpartum haemorrhage, an important cause of maternal death. Oxytocin is widely available in low and middle-income countries (LMIC) but there are concerns about its quality.

Objective To identify, critically appraise and synthesise the findings of studies on the quality of oxytocin available in LMIC.

Search strategy We searched seven electronic databases, without language restriction.

Selection criteria Studies reporting results of tests to assess quality of oxytocin samples from LMIC.

Data collection and analysis Study selection, data extraction and quality assessment were performed in duplicate. Results are presented descriptively.

Main results The search identified 2611 unique citations; eight studies, assessing 559 samples from 15 different countries were included. Most samples were collected from facility level settings ($n = 509$) and from the private sector ($n = 321$). The median

prevalence of oxytocin samples that failed quality tests was 45.6% (range 0–80%), mostly due to insufficient amounts of active pharmacological ingredient. Over one-third of the samples ($n = 204$) had low (<90%) oxytocin content indicating substandard medicine; two samples had no active ingredient, suggesting possible counterfeit drugs. The proportion of low fails was higher in samples collected in Africa than in Asia or Latin America (57.5% versus 22.3% versus 0%, respectively, $P < 0.0001$), in private than in public sectors (34.0% versus 25.3%, $P = 0.032$) and in facilities than in central distributors (37.9% versus 22.0%, $P = 0.030$).

Conclusion There is a high prevalence of poor-quality oxytocin samples in LMIC countries, mainly due to inadequate amounts of active ingredient.

Keywords Low and middle-income countries, oxytocin, postpartum haemorrhage, quality, sterility.

Tweetable abstract Systematic review points to problems with quality of oxytocin samples from low- and middle-income countries.

Please cite this paper as: Torloni MR, Gomes Freitas C, Kartoglu UH, Metin Gülmezoglu A, Widmer M. Quality of oxytocin available in low- and middle-income countries: a systematic review of the literature. BJOG 2016; DOI: 10.1111/1471-0528.13998.

Introduction

Every year, an estimated 480 000 women die due to bleeding complications related to pregnancy and childbirth.¹ Postpartum haemorrhage (PPH) remains the leading direct cause of maternal mortality worldwide, representing 27.1% of all maternal deaths.¹ The use of uterotonics plays an important role in the prevention and treatment of PPH.

Oxytocin is recommended by the World Health Organization (WHO) as the uterotonic drug of choice for the prevention and treatment of PPH.² Oxytocin is included in the WHO Essential Medicines list, as well as in the United Nations Commission on Life-Saving Commodities for Women and Children (UNCoLSC) list. Oxytocin is widely available in low- and middle-income countries (LMIC) but there are many concerns about its quality.³ This can be due to low manufacturing quality or inadequate transport and storage conditions along the supply chain, or both.⁴ Oxytocin needs to be stored under refrigeration (2–8°C) as

The copyright line for this article was changed on 11 April 2016 after original online publication.

much as possible, although short periods of unrefrigerated transport not exceeding 1 month at 30°C or 2 weeks at 40°C, are acceptable.⁵ Oxytocin should also not be frozen, although recent evidence suggests that multiple cycles of freezing and thawing do not significantly change oxytocin content.⁶ Although several studies and reports have assessed the quality of oxytocin in LMIC, their findings have not been analysed or synthesised. The objective of this systematic review was to identify, critically appraise and synthesise the findings of studies on the quality of oxytocin commercially available in LMIC countries.

Methods

This review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statements.^{7,8} We did not register a protocol for this systematic review.

The quality of medicines includes many aspects directly related to the product itself (e.g. appearance, volume, pH, pharmaceutical content, sterility, related substances, contaminants, solubility), as well as aspects related to packaging, labelling, transportation and storage conditions of the product, including light, humidity and temperature of the area where the product is kept. We report failure rates of oxytocin samples according to the parameters assessed by the authors of each included study. However, we focus on two main aspects of oxytocin quality, namely active pharmacological ingredient (API) and sterility, essential attributes of this injectable thermolabile drug, that are also the most frequently reported in primary studies on medicine quality. According to the International Pharmacopoeia, oxytocin injections should contain not less than 90% and not more than 110% of the amount of oxytocin ($C_{43}H_{66}N_{12}O_{12}S_2$) stated on the label and should be sterile.⁹ These limits are also used by the British Pharmacopoeia and US Pharmacopoeia. Therefore, for all these pharmacopoeias as well as for regulatory authorities and manufacturers that registered these limits, products containing less than 90.0% or over 110% oxytocin would be considered substandard and not to be used in treatment.

For the purpose of this review, oxytocin samples were considered of inadequate quality if the level of API did not reach 90% of the stated content (low fail), or was higher than 110% (high fails). Although the administration of large doses of highly concentrated oxytocin with large volumes (usually over 3–4 l) of intravenous liquids devoid of electrolytes (e.g. 5% dextrose) can in theory lead to severe adverse effects due to hyponatraemia, these events are rare.¹⁰ Therefore, the main focus of our review was on the rate of oxytocin samples with less than the stated amount (low fails), since it is logical to assume that the injection of

products containing less than the minimum recommended active ingredients can compromise the effectiveness of the drug in the prevention or treatment of PPH. Sterility of an injectable product is also an important quality parameter and we report the results of this test for all of the samples, if provided by the authors, in isolation or combined with the results of oxytocin quantification assays. Samples with adequate oxytocin content (i.e. API 90–110%) but that failed sterility tests were considered of poor quality.

All studies that provided assays of injectable oxytocin quantification (API) and/or sterility, using any valid laboratory method were eligible for inclusion. Studies that also reported the results of other tests (e.g. pH, contaminants, impurities, packaging status or storage temperature) were eligible for inclusion as long as they also provided separate information on oxytocin quantification and/or sterility tests. Studies assessing samples collected from the public or private sector, at facilities (e.g. hospitals, clinics, local medical stores or pharmacies, informal vendors or markets) or central distributors (e.g. warehouses, major distributors or central medical stores) were eligible for inclusion. Outlets run by non-governmental organisations (NGO) were categorised as private.

Editorials, reviews or commentary papers were excluded from this review. We did not include studies on analytical methods for the identification of oxytocin, or studies that only assessed storage conditions or simulation studies, which created artificial conditions to test the effects of heat, light or other factors on oxytocin quality.

Process of study identification and data extraction

We searched the literature for all published studies or reports that described the quality of oxytocin samples collected in LMIC countries, regardless of sample size or date of publication. The following electronic databases were searched, from inception up to March 2015, without language restrictions: EMBASE, PUBMED/MEDLINE, African Index Medicus (AIM), International Pharmaceutical Abstracts (IPhA), LILACS, IBECs and Cochrane. The search strategy was created with the help of a librarian experienced in systematic reviews and included the terms ‘oxytocin’ AND ‘post-partum haemorrhage’ and synonyms (see Supplementary material, Appendix S1, for the full search strategy). The search was complemented by reviewing the list of references of all articles selected for full text reading and by looking for unpublished studies or reports through contacts with investigators who had conducted or were conducting studies on oxytocin quality and with WHO staff.

Citations were downloaded using a reference manager software (ENDNOTE version X7; Thomson Reuters, New York, NY, USA) into a single file and duplicates were excluded. The titles and abstracts of all unique citations were screened and those that were potentially eligible were

selected for full text reading. The full text articles were obtained and assessed for inclusion based on the aforementioned selection criteria. The following data were extracted from included studies: geographical location and year of sample collection, types of outlets where samples were collected (public versus private sector, central versus facility level), origin of the drugs (manufacturer and country), types of tests performed, number of sample assayed and number of samples failed according to the authors' criteria, number of samples failed due to inadequate (low or high) API and to lack of sterility. Two independent reviewers (MRT and CG) performed the process of study selection and data extraction; disagreements were discussed until consensus was reached.

Assessment of the quality of the studies

We assessed the methodological quality of all included studies using the criteria proposed by Almuzaini et al.¹¹ based on the methodology section of the MEDQUARG (Medicine Quality Assessment Reporting Guidelines) checklist for reports of surveys of medicine quality.¹² Basically, each study was graded on 12 domains: (1) survey details, (2) definitions of substandard medicines, (3) types of outlets sampled, (4) sampling design and sample size calculation, (5) type and dosage of units collected per outlet, (6) random sampling, (7) details of samplers, (8) packaging assessment, (9) statistical methods, (10) chemical analysis description, (11) method validation details and (12) blinding of chemical assessors (see details in Supplementary material, Appendix S3). Two independent reviewers (MRT and CG) graded the quality of each study, compared their scores and discussed discrepancies until consensus was reached on a final grade for each study. There were no established cut-offs, so studies with a grade of 6 or more were categorised as being of good quality, as proposed by a previous review.¹¹

Data synthesis and statistical analyses

We first present the total rate of failed samples in general, as reported by the authors. We decided not to pool the proportion of failed samples into a meta-analysis because this definition was heterogeneous in the primary studies. We then present the prevalence of samples failed because of inadequate amount of active ingredient (API <90% or >110%), the prevalence of low fails (API <90%) and high fails (API >110%) per study and according to geographical location (continents) and type of outlets where the samples were collected. We performed subgroup analyses of samples with low API content collected in public versus private sector outlets, as well as central versus facility-level settings. The countries providing samples were classified according to the World Bank as low income (LIC), lower middle income (LMIC), upper middle income (UMIC)

countries.¹³ The chi-square and two-sided Fisher exact tests were used for statistical analyses. $P < 0.05$ was considered significant.

Results

A total of 2611 unique citations were identified through various sources, 22 studies were selected for full text reading, 14 were excluded for different reasons (see Supplementary material, Appendix S2) and eight records were included in the review^{5,14–20} (Figure 1). Two were articles published in peer-reviewed journals^{17,18} five were unpublished reports available online in various institutional sites^{3,5,14,19,20} and one was a congress abstract.¹⁶ We obtained additional (unpublished) details from the authors of five reports.^{5,14,16,19,20} The eight included studies reported on the collection and analyses of 559 samples from 15 different countries: five studies included only LMIC,^{14,16–18,20} one study only a LIC,⁵ one study an UMIC¹⁹ and one study included LIC and LMIC¹⁵ (Table 1).

The final methodological quality scores of the studies ranged from 2 to 9, out of a maximum of 12 (mean 5.8 ± 2.4 , standard deviation) and four of the eight studies were considered of good methodological quality (scores ≥ 6).^{14,16–18} Almost all studies scored highly on the domains related to the description of the type of outlet sampled (domain 3), the location and timing of the study (domain 1) and the chemical analyses performed (domain 10) but none provided details about the methods used to validate the chemical tests performed (domain 11). The domains with the lowest scores were those related to the description of statistical techniques used for data analyses (domain 9), blinding of chemical assessors (domain 12) and number of dosage units obtained from individual outlet (domain 5) (see Supplementary material, Appendix S3).

The eight studies assayed a total of 559 oxytocin samples, ranging from 5⁵ to 193¹⁸ samples per study (median 34 samples per study, interquartile range 7.5–124.7) (Table 2). Ghana was the country with the largest individual number of samples ($n = 215$),^{14,17} followed by India¹⁸ ($n = 193$), while Kenya, Madagascar and Burkina Faso contributed with only one sample each.¹⁵ The manufacturers of 559 samples included in the eight studies were from 13 different countries, with several different manufacturers in each country. The three countries which manufactured the largest numbers of oxytocin samples were India,^{3,18} China^{3,14,19} and Indonesia,¹⁶ which produced 36.0% ($n = 201$), 26.6% ($n = 149$) and 19.7% ($n = 110$) of the total samples each, respectively (see Supplementary material, Appendix S4). Most of the samples were collected at facility level settings (91%, $n = 509$) and from the private sector (57.4%, $n = 321$). Five of the studies^{3,14,16,19,20} performed additional tests besides oxytocin quantification

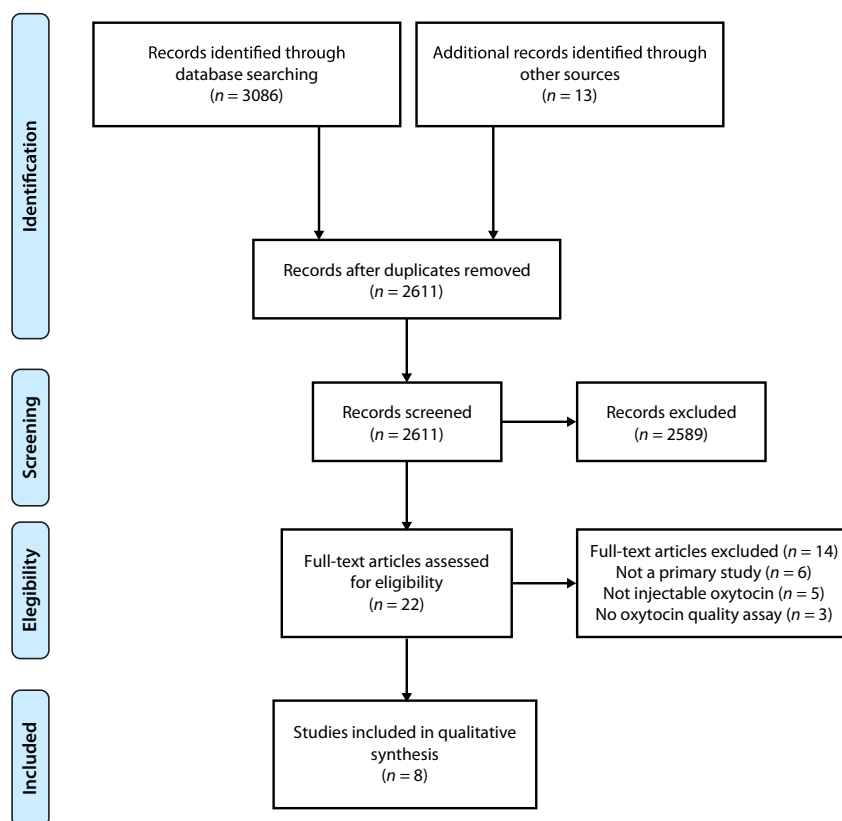


Figure 1. Process of study identification and selection.

assays, including tests for sterility, contaminants or strange particle matters and pH (Table 2, and see Supplementary material, Appendix S5).

The median prevalence of oxytocin samples that did not pass quality testing, as defined by various parameters adopted by the original authors, was 45.6% (range 0–80%, interquartile range 8.8–66.7%). The median prevalence of oxytocin with inadequate API content was 36.0% (range 0–80%, interquartile range 8.8–60.7%, $n = 223$) and most failures ($n = 204$) were due to low (<90%) API content (Table 2). Only 19 of the 559 samples (3.4%) failed because of excessively high (>110%) oxytocin content. The study with the highest rate of high fails was conducted in Zimbabwe and included only five samples of oxytocin collected in 1992, which were imported from unspecified countries; four of these (80%) failed due to API content >110%.⁵ Two more recent studies, from India¹⁸ and Indonesia,¹⁶ also reported a small number of oxytocin samples with API >110% ($n = 12$ of 193 and $n = 3$ of 110, respectively); the medicine in both studies was manufactured by local companies (see Supplementary material, Appendix S5).

The concentration of oxytocin in the 204 samples with low API ranged from 0%^{14,16} to 89.8%.¹⁵ Most (48/69) of the failed samples from India had between 76 and 89% content¹⁸ and most (19/35) of the low fail samples collected in Ghana by Stanton et al.¹⁷ in 2010 had 60–89% API. The eight failed samples from the multi-country study had oxytocin concentrations between 50 and 89%.¹⁵ There were only two samples, one from Indonesia¹⁶ and one from Ghana,¹⁴ with 0% API, which is an indication of possible counterfeit drug. These same two studies did not provide the exact oxytocin concentration for their other low-fail samples ($n = 12$ and $n = 93$, respectively).

Table 3 presents the proportion of failed samples according to their provenance. The proportion of low fails (API <90%) was significantly higher in the private than in the public sector samples (34.0% versus 25.9%, respectively, $P = 0.032$). Similarly, the proportion of low fails was significantly higher in samples from facilities than from central level settings (37.9% versus 22.0%, $P = 0.030$). There is no information suggesting that the oxytocin samples collected at facility level were from the same batch and manufacturer as the oxytocin samples collected at central level.

Table 1. Overview of main characteristics of studies on quality of oxytocin

Characteristic	N of studies	References
Region		
Africa	3	5,14,17
Asia	2	16,18
Latin America	2	19,20
Mixed (Asia and Africa)	1	15
Country income level		
UMIC	1	19
LMIC	5	14,16,17,18,20
LIC	1	5
Mixed (LMIC and LIC)	1	15
Year of sample collection		
Before 2011	3	5,17,19
2011 or after	5	14,15,16,18,20
Total N of samples analysed		
<10	3	5,19,20
11–99	2	15,17
≥100	3	14,16,18
Type of sector of sample collection		
Private only	1	18
Public only	2	5,16
Both	5	14,15,17,19,20
Setting of sample collection		
Central level* only	1	15
Facility level** only	4	5,17,18,19
Both	3	14,16,20
Country of oxytocin manufacturer		
National	2	16,18
Imported	5	5,14,15,19,20
No information	1	17
Methodological quality of study***		
High risk of bias	4	5,15,19,20
Low risk of bias	4	14,16,17,18

*Central level facility: warehouses, major distributors or central medical stores.

**Facility-level settings: hospitals, clinics, local medical stores or pharmacies, informal vendors or markets.

***High risk is <6 points and Low risk is ≥6 points on a scale of points assigned to 12 domains of MEDQUARG Checklist as recommended by Almuzaini et al.¹¹

The 235 oxytocin samples from the eight African countries (Ghana, Zimbabwe, Burkina Faso, Kenya, Madagascar, Nigeria, Tanzania and Uganda) had the highest rates of low failures, with almost 58% of the samples ($n = 135$) having oxytocin concentrations <90% of the stated content. All of the 235 samples collected in Africa were imported from other countries, mostly China. The 310 samples collected in Asia (India, Indonesia, Nepal, Tajikistan and Vietnam) had a 22.3% failure rate ($n = 69$). All the 14 samples from two Latin American countries (Peru and Guatemala) passed the oxytocin quantification assay (i.e. API between

90 and 110%). The proportion of failed samples was significantly higher in Africa than in Asia or Latin America (57.5% versus 22.3% versus 0%, respectively, $P < 0.0001$).

Only three studies provided the results of both API content and sterility tests for their samples. The six oxytocin samples collected in Guatemala²⁰ and the eight samples from Peru¹⁹ passed both tests. The third study¹⁴ assayed a total of 169 samples in Ghana and 94 failed due to low API. Due to resource constraints, the authors randomly selected 40 samples (out of the 169) and performed sterility tests only in this subset. The investigators report that 97.5% of these samples failed either the API or sterility or both tests.

Discussion

Main findings

This review found a relatively small number of studies that assessed the quality of oxytocin samples in LMIC. The analyses of these samples reveal a high prevalence of poor quality oxytocin in LMIC countries, especially in Africa and Asia, and the main problem is insufficient amount of active ingredient. Over one-third of the 559 samples tested in the eight studies included in this review had oxytocin content below the minimum (90%) stated amount, indicating substandard medicine and two samples had no active ingredient, possibly corresponding to counterfeit drugs. The proportion of low fails was highest in Africa, where almost 60% of the samples assayed had <90% of the oxytocin quantity stated in the ampoules. Samples collected in the private sector and in end-point facilities had higher proportions of low API content than those collected in the public sector or in central facilities. Few studies, involving a small number of samples, performed sterility tests and reported a high rate of samples failing either the API or sterility or both tests.

Strengths and limitations

This is the first systematic review on the quality of injectable oxytocin in LMIC. Bias was reduced by using a strict methodology including duplicate study selection, data extraction and quality assessment. We used a broad search strategy without language restriction and we tried to identify unpublished reports striving to reduce publication bias. However, although most (six of the eight) of our included studies were not papers published in peer-reviewed journals but reports, as the concern for oxytocin quality is growing, there might exist additional unpublished studies that were not identified and therefore not included in this review. We may also have missed studies with completely favourable results (all samples of good quality) because they may have more difficulty in getting published (publication bias). Finally, it is possible that we did not have access to studies with very unfavourable results (high rates of failed

Table 2. Main characteristics and findings of eight studies on quality of oxytocin samples from LMIC countries

Reference	Country (Economic classification)	Year sample collection / testing	Study quality / grade*	Total N of samples assayed	Country of manufacturer (N of samples)	Provenience of sample (N of samples from central or facility level setting and public or private sector outlets)	Tests performed	Percent failed samples**	Stated problem	Percent inadequate API Fails***, % (n)	Percent low API fails****, % (n)
Stanton (2012) ¹⁷	Ghana (LMIC)	2010	8	46	NI	46 facility level settings 33 private, 12 public sector, 1 NI	API	76.1	Inadequate API	76.1 (35)	76.1 (35)
Karikari (2013) ^{14,*****}	Ghana (LMIC)	2012	8	169	China (141) Pakistan (4) Switzerland (3) NI (21)	162 facility level, 7 central level settings 90 public, 79 private sector	API, sterility tests (only 40 samples)	55.6 (API) 97.5 (API or sterility or both, n = 40)	Inadequate API or not sterile or both	55.6 (94)	55.6 (94)
Stanton (2014) ¹⁸	India (LMIC)	2011	9	193	India (193)	193 private sector facility level settings	API	35.7	Inadequate API	35.7 (69)	29.5 (57)
Hogerzeil (1993) ^{5,*****}	Zimbabwe (LIC)	1992	4	5	Unclear ('imported')	5 public facility level settings	API	80.0	Inadequate API	80.0 (4)	0
Pribluda (2012) ^{16,*****}	Indonesia (LMIC)	2011	7	110	Indonesia (110)	91 facility level 19 central level settings	API, identity, contaminant or strange particle matters	11.8	Inadequate API or no API or contaminants	11.8 (13)	9.1 (10)
Medicines Quality Database (2011) ^{20,*****}	Guatemala (LMIC)	2011	3	6	Mexico (5) El Salvador (1)	110 public sector settings 4 facility level, 2 central level settings 5 public, 1 private sector	API, sterility, endotoxin, pH, volume in ampoule	0	None	0	-
Medicines Quality Database (2010) ^{19,*****}	Peru (UMIC)	2010	2	8	Chile (3), China (2), Peru (2), Ignored (1)	8 facility level settings 6 public, 2 private sector	API, sterility, endotoxin, pH, volume in ampoule	0	None	0	-

Table 2. (Continued)

Reference	Country (Economic classification)	Year sample collection / testing	Study quality grade*	Total N of samples assayed	Country of manufacturer (N of samples)	Provenience of sample (N of samples from central or facility level setting and public or private sector outlets)	Tests performed	Percent failed samples**	Stated problem	Percent inadequate API Fails***, % (n)	Percent low API fails****, % (n)
UN Col LSC (2015) ¹⁵	10 countries (6 LIC, 4 LMIC)	2013	5	22	India (8), China (6), Germany (5), Russia (1), Hungary (1), Italy (1)	22 central level settings 13 private, 9 public sector	API, identity, appearance, pH, volume, related substances	63.6	Inadequate API or no API or presence of related substances or visible particles	36.4 (8)	36.4 (8)
Total	15 countries	1993 to 2013	5.8 (2.4) *****	559	13 countries	Facility level settings: 509 (91%) Private sector: 321 (57.4%)	—	45.6% (8.8, 66.7) *****		36.0% (8.8, 60.7) *****	32.9% (14.2, 50.8) *****

NI, not informed; UN Col LSC, United Nation Commission on Life-Saving Commodities for Women and Children.

*Maximum grade of 12 on MEDQUARG Checklist (Newton et al.¹², Almuzaini et al.¹¹).

**Failure as defined by the authors.

***API <90% or >110%.

****Low fail: API <90% of stated content.

*****Additional (unpublished) information provided directly from authors.

*****Mean (standard deviation).

*****Median % (first, third quartile %).

Table 3. Rates of low failure* of 559 oxytocin samples collected in LMIC countries, according to source

Study	Country	All samples			Public sector samples			Private sector samples			Central level** samples			Facility-level*** samples			
		Total		Low fails*	Total		Low fails*	Total		Low fails*	Total		Low fails*	Total		Low fails*	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Stanton (2012) ¹⁷	Ghana	46	35	76.1	124	NI	NI	33	NI	NI	0	0	0	0	46	35	76.1
Karikari (2013) ¹⁴	Ghana	169	945	55.6	90	48	53.3	79	46	58.2	7	3	42.9	162	91	56.2	
Stanton (2014) ¹⁸	India	193	57	29.5	0	0	0	193	57	29.5	0	0	0	193	57	29.5	
Hogerzeil (1993) ⁵	Zimbabwe	5	0	0	5	0	0	0	0	0	0	0	0	5	0	0	
Pribluda (2012) ¹⁶	Indonesia	110	10	9.1	110	10	9.1	0	0	0	19	0	0	91	10	11.0	
MQ Database (2011) ²⁰	Guatemala	6	0	0	5	0	0	1	0	0	2	0	0	4	0	0	
MQ Database (2010) ¹⁹	Peru	8	0	0	6	0	0	2	0	0	0	0	0	8	0	0	
UN Col LSC (2015) ¹⁵	Burkina Faso, Kenya, Madagascar, Nepal, Nigeria, Tajikistan, Tanzania, Uganda, Vietnam, Zimbabwe	22	8	36.4	9	2	22.2	13	6	46.2	22	8	36.4	0	0	0	
Total		559	204	36.5	237	60****	25.3	321	109*****	34.0	50	11	22.0	509	193	37.9*****	

MQ Database, Medicine Quality Database; UN Col SLC, United Nation Commission on Life-Saving Commodities for Women and Children.

*Low failures: API <90%.

**Central level: warehouses, major distributors or central medical stores.

***Facility level: hospitals, clinics, local medical stores or pharmacies, informal vendors or markets.

****One sample did not have information on type of sector (private or public).

*****Two samples (from private facility level settings) had 0% API content.

samples), which may have not been made publically available by national authorities. An additional limitation of our review is that half of the included studies were of poor methodological quality, mainly due to lack of information on key details (e.g. methods used to validate the chemical tests used or statistical analyses). This seems to be indicative of poor reporting quality and does not necessarily reflect poor methodological quality of the studies. Our focus on two specific aspects of quality, namely API content and sterility, is also a potential additional limitation of this review. Although other aspects of product quality (e.g. pH, solubility, contaminants, labelling) are part of standard processes for medicine quality assessment, these parameters are seldom reported by most primary studies.

Interpretation

This systematic review could not identify the specific causes for the low quality of the oxytocin samples assessed. Since most of the samples from the eight studies were collected at periphery-level facilities, it is difficult to conclude whether the low quality of the oxytocin was due to problems at the manufacturer level, inadequate storage conditions during distribution or at the facilities, or a combination of these problems. None of the studies provided information on how long the ampoules had been stored in the central or facility-level settings and under what conditions of temperature they had been stored over time. As product degradation is related to the time spent under suboptimal conditions, this information is highly relevant.

Further research is needed to assess the factors and potential causes that may affect the quality of the oxytocin currently available in LMIC countries. Future studies conducted at the country of origin should assess the manufacturing quality of oxytocin and product regulation by the regulatory authorities. We also need studies that follow the product along the supply chain to identify whether temperature changes affect the quality of oxytocin. A study involving both of these assessments is currently being conducted in Ghana, in collaboration with the WHO.

One approach to identify the oxytocin ampoules that were exposed to high temperatures is to include temperature-time indicators (TTI) in the oxytocin ampoules. TTIs indicate excessive heat exposure over time and therefore allow health workers to make better-informed decisions on the extent to which heat has affected the product and whether to use the oxytocin ampoules or not. TTIs mimic the degradation of the pharmaceutical product against time and temperature with a safety margin, and are calibrated against the stability characteristics of a product. Vaccine vial monitors (VVM = TTI for vaccines) have been used for all WHO prequalified vaccines since 1996 and are included among the minimum requirements in all interna-

tional tenders by all United Nations procurement agencies and any member states.^{21,22} A simulation study involving TTIs with oxytocin used VVM type 30 (meaning that VVM will reach its discard point in 30 days if kept at 37°C constant temperature), found that a considerable number of oxytocin samples were rejected although they were still within acceptable specifications.²³ However, we must note that VVM is not a potency indicator and is designed to warn health workers on the impact of time and temperature on the product with a reasonable safety margin. In addition, when it is decided to have TTIs for oxytocin, the temperature sensitivity of the product should be studied to match the best TTI category—which may not correspond to VVM30.²⁴

All included studies except one⁵ assayed samples collected since 2010, showing that the quality of oxytocin is increasingly becoming a global concern. If the samples obtained in the studies included in this review are representative of what is currently available in LMIC countries, for every three women who receive oxytocin in these settings, at least one will receive an injection that contains less than the expected amount of the medicine and will therefore be denied the effects of this potentially life-saving medicine.

Most of the samples collected in the two largest studies conducted in Africa^{14,17} were from non-registered manufacturers. Moreover, none of the samples analysed in all the included studies are WHO-prequalified oxytocin products. The registration of a product in a country ensures the safety, efficacy and the quality of the drugs, and the WHO prequalification process helps to identify quality drugs from countries. However, to achieve prequalification, producers need to improve the manufacturing process and consequently increase the price of the product. Therefore, as highlighted in the Jhipiego business case⁴ governments must incentivise manufacturers to produce high-quality oxytocin without losing competitively against non-quality-assured drugs. On the other hand, having oxytocin included in the WHO prequalification list is helpful to procurement agencies to identify quality products. Globally, approximately 100 million doses per year are used for prevention and treatment of PPH and there are at least 300 different oxytocin products manufactured, creating a market that is difficult to regulate.⁴

Conclusion

There is a widespread problem with the quality of oxytocin samples from LMIC countries, especially in Africa and Asia. This can potentially be a contributing factor to the high rates of maternal morbidity and mortality in these settings. Future studies are needed to identify the exact factors involved in the low quality of oxytocin in LMIC countries and to plan appropriate interventions to improve this situation.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

MW, AMG and UHK suggested the research question. MRT and CGF designed the study, conducted the search, and extracted and analysed data. MRT drafted the article and all other authors revised the content contributing substantially.

Details of ethics approval

No ethics approval was necessary for this review, as no patient data were used.

Funding

The study was supported by a grant from Merck Sharp and Dohme Corp., a wholly owned subsidiary of Merck and Co., Inc. (Kenilworth, NJ, USA), through its Merck for Mothers programme, to UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research, World Health Organization. The funder was not involved in the design, data collection, analysis, interpretation or writing of this report, nor the decision to submit the article for publication.

Acknowledgements

We are grateful to the authors who contributed additional information on their publications. We are also grateful to Maria Eduarda Puga, who contributed to the design of the search strategy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategy.

Appendix S2. List of excluded studies.

Appendix S3. Quality scores of studies.

Appendix S4. Country of origin of oxytocin sample manufacturers.

Appendix S5. Details of included studies. ■

References

- Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Global health* 2014;2:e323–33.
- World Health Organization. WHO recommendations for the prevention and treatment of postpartum haemorrhage. 2012 [http://apps.who.int/iris/bitstream/10665/75411/1/9789241548502_eng.pdf]. Accessed 15 October 2015.
- UN Commission on Life-Saving Commodities for Women and Children. Commissioners Report September 2012 [www.unfpa.org/sites/default/files/pub-pdf/Final%20UN%20Commission%20Report_14sept2012.pdf]. Accessed 15 October 2015.
- Jhpiego. Business case: investing in production of high-quality oxytocin for low-resource settings – final report December 2014 [www.conceptfoundation.org/wp-content/uploads/2015/06/Business_Case_Oxytocin_web.pdf]. Accessed 15 October 2015.
- Hogerzeil HV, Walker GJA, De George MJ. *Stability of Injectable Oxytocics in Tropical Climates: Results of Field Surveys and Simulation Studies on Ergometrine, Methylergometrine and Oxytocin*. Geneva: WHO Action Programme on Essential Drugs, 1993.
- Nassta GC, Pranker RJ, McIntosh MP. Effect of freezing on oxytocin ampules. *N Engl J Med* 2013;368:2145–6.
- Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
- Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008–12.
- World Health Organization Department of Essential Medicines and Health Products. International pharmacopoeia – 4th supplement. 2014 [http://apps.who.int/phint/en/p/about/]. Accessed 10 August 2015.
- Ophir E, Solt I, Odeh M, Bornstein J. Water intoxication—a dangerous condition in labor and delivery rooms. *Obstet Gynecol Surv* 2007;62:731–8.
- Almuzaini T, Choonara I, Sammons H. Substandard and counterfeit medicines: a systematic review of the literature. *BMJ Open* 2013;3:e002923.
- Newton PN, Lee SJ, Goodman C, Fernandez FM, Yeung S, Phanouvong S, et al. Guidelines for field surveys of the quality of medicines: a proposal. *PLoS Med* 2009;6:e52.
- World Bank. How we classify countries. 2015 [http://data.worldbank.org/about/country-and-lending-groups]. Accessed 15 October 2015.
- Karikari-Boateng E. *Post-Market Quality Surveillance Project Maternal Health Care Products (Oxytocin and Ergometrine) on the Ghanaian Market*. Accra, Ghana: Ghana Food and Drugs Authority, 2013.
- World Health Organization Prequalification Team (WHO PQT). *Survey of the Quality of Medicines Identified by the UN Commission on Life-Saving Commodities for Women and Children*. Geneva: World Health Organization, 2015.
- Pribluda VS, Phanouvong S, Villadiego S, Rooslamati I, Setiawati A. Quality of oxytocin injections: a case study in Indonesia. Congress Abstract, Asia Regional Meeting on Interventions for Impact in Essential Obstetric and Newborn Care, May 3–6 2012, Dhaka, Bangladesh; 2012.
- Stanton C, Koski A, Cofie P, Mirzabagi E, Grady BL, Brooke S. Uterotonic drug quality: an assessment of the potency of injectable uterotonic drugs purchased by simulated clients in three districts in Ghana. *BMJ Open* 2012;2:e000431.
- Stanton C, Nand DN, Koski A, Mirzabagi E, Brooke S, Grady B, et al. Accessibility and potency of uterotonic drugs purchased by simulated clients in four districts in India. *BMC Pregnancy Childbirth* 2014;14:386.
- Medicines Quality Database. Quality of oxytocin samples Peru. 2010 [www.usp.org/global-health-programs/promoting-quality-medicines-pqmusaidd/medicines-quality-database-mqdb]. Accessed 15 October 2015.

- 20** Medicines Quality Database. Quality of oxytocin samples Guatemala. 2011 [www.usp.org/global-health-programs/promoting-quality-medicines-pqmusaid/medicines-quality-database-mqdb]. Accessed 15 October 2015.
- 21** World Health Organization. WHO-UNICEF policy statement on the implementation of vaccine vial monitors: The role of vaccine vial monitors in improving access to immunization. 2007 [www.who.int/immunization_standards/vaccine_quality/VVM_joint_statement_2007.pdf?ua=1] Accessed 15 October 2015.
- 22** Frost LJ, Reich M. *Access: How Do Good Health Technologies Get to Poor People in Poor Countries?* Chapter 7. Vaccine Vial Monitor. Cambridge, MA: Harvard Center for Population and Development Studies: Harvard University Press, 2009.
- 23** Mullany LC, Newton S, Afari-Asiedu S, Adibokah E, Agyemang CT, Cofie P, et al. Cumulative effects of heat exposure and storage conditions of Oxytocin-in-Uniject in rural Ghana: implications for scale up. *Glob Health Sci Pract* 2014;2:285–94.
- 24** Hodgins S. Oxytocin: taking the heat. *Glob Health Sci Pract* 2014;2:259–60.