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Stability of oxytocin along the supply chain: A WHO observational study

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ABSTRACT

Postpartum haemorrhage is the leading cause of maternal mortality in low-income countries and oxytocin is the drug recommended by WHO for preventing and treating it. There are concerns about the quality of oxytocin available at the service level provider. The study aimed to document how temperature variations along the supply chain affect quality of oxytocin. The study was run from March to June 2015 in four regions of Ghana. 130 ampoules of oxytocin were shipped from the manufacturer to service level following Ghanaian public sector supply chain. Along the supply chain, temperatures were recorded continuously. After one month storage at central, regional and service level, ampoules were sent to laboratory for testing. Quality of the initial oxytocin sample from the manufacturer and the 130 oxytocin samples received from study points were tested according to International Pharmacopeia monograph. Samples fully complied with specifications. Temperature profile showed that the lowest and highest temperatures experienced were −9.9 °C and +30.1 °C. The results of this study indicate that the activity of oxytocin was not affected by these temperature excursions which occurred along the supply chain. The quality of the oxytocin from the manufacturer as well as from the service level was within the required specifications.

1. Introduction

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality in low-income countries and the primary cause of nearly one quarter of all maternal deaths globally [1]. The use of uterotonics plays a central role in the prevention and treatment of PPH and oxytocin is recommended by the World Health Organization (WHO) as the first drug of choice for these situations [2].

Despite oxytocin being a well-known and extensively studied peptide hormone, included in the Essential Medicines list (EML), in the life-saving commodities list developed by the United Nations Commission on Life-Saving Commodities for Women and Children's Health (UNCoLSC) [3] as well as in the reproductive health commodities listed under the WHO prequalification system, there is limited information on its stability at tropical temperatures, especially in extreme climate conditions. Oxytocin needs to be stored under refrigeration (2–8 °C), although short periods of unrefrigerated transport not exceeding one month at 30 °C or 2 weeks at 40 °C, are acceptable [4]. It is also recommended that the product should not to be frozen. Though, one study reported that multiple cycles of freezing and thawing produced no significant changes in the oxytocin content [5].

Several studies looked at the quality of oxytocin at the point of sale and found that in many places the active pharmaceutical ingredient (API) was below the specifications [6]. Possible causes for substandard oxytocin ampoules include quality of manufacturing and inappropriate conditions during the supply chain (system of organizations, people, activities, information, and resources involved in moving a product from the supplier to end user in a manner that ensures the good quality of the product until it is consumed [7]).

The UNCoLSC, with the aim of increasing the access to and appropriate use of medicines that effectively address leading avoidable causes of death during pregnancy, ran a survey focused

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on selected medicines including oxytocin, to identify manufacturers of certified quality [8]. Although this survey detected oxytocin products that were outside specifications already at central level, the study could not assess the quality of the oxytocin along the supply chain.

We, therefore, conducted an observational study in Ghana to evaluate how temperature variations, during the distribution of oxytocin ampoules from the manufacturer to the health-care providers, affected the amount of active oxytocin ingredient (API).

Results of this study may contribute towards building strategies in sustaining the quality of the product at the point of use.

2. Material and methods

The design of this study was based on the WHO study protocol for temperature monitoring in the vaccine cold chain [9]. Briefly, temperatures are monitored continuously as shipments travelled through the cold chain, from central stores, to intermediate stores, to health centres or service points. The study was done in collaboration with United Nations Population Fund (UNFPA) and the WHO country office in Ghana.

The study was implemented in Ghana, where temperatures exceed 29 °C during several months in the year. The oxytocin studied was the one used in the highest volume by the Ministry of Health in Ghana in the year 2014 and with a quality, tested at Ghana Central Store, within acceptable ranges (*UNCoLSC survey*). The supply chain study route was the one used by UNFPA and included all levels between the manufacturer of the product and eight service points (four rural and four urban) from four randomly selected regions in Ghana. Following local standard practice, the storage duration of the oxytocin at each level of the supply chain was set at one month. After one month of storage the ampoules were sent to an ISO17025 accredited laboratory in Accra, Ghana for analysis.

The study pack containing a total of 130 oxytocin ampoules (13 boxes of 10 ampoules of oxytocin 10 IU/ml each, all from the same manufacturer's production batch) was dispatched as part of the big oxytocin shipment ordered by UNFPA from the manufacturer in Germany through a distributor in The Netherlands, to Ghana Central Store and then on to four regions and to eight health centres (service points) under controlled temperature of 2 °C–8 °C as per manufacturer's indication.

Ambient temperatures and temperatures inside the oxytocin boxes were recorded using electronic data loggers and vaccine vial monitors (VVM) continuously from the manufacturer until the time the oxytocin ampoules reached the laboratory for analysis.

A data logger is a continuous temperature monitoring device with a recording accuracy of ± 0.3 °C programmed to record temperature every 10 min. A VVM is a circular indicator printed on a card with an inner square made of heat-sensitive material that is initially light in color and becomes darker when exposed to heat over time.

At the manufacturer, one electronic data logger (TRIX8 LogTag recorder) was placed inside the study pack and another TRIX8 LogTag recorder was attached to the outer surface of the pallet shipper (a combination of products stacked together and shrink-wrapped on a pallet for shipment to a retailer).

Upon arrival at the distributor facility, the study pack was separated from the pallet but was kept in the cold room (2–8 °C) along with the rest of the shipment. Two investigators visited the distributor facility and prepared 13 individual study packs. Each of these packs consisted of a box containing 10 oxytocin ampoules, one TRIX8 LogTag recorder, one vaccine vial monitor (VVM) card including two different type VVMs as VVM14 and VVM30 [10] and one recording form. A second TRIX8 LogTag recorder was attached outside of the individual study pack with a rubber band. The investigators then labeled each box with its final destination (service point).

The individual study packs were placed inside cartons which were then labeled with the name of the four regions participating in the study. Each carton contained two individual study packs for service points, one study pack marked “LAB” (sample for laboratory analysis) and one TRIX8 LogTag recorder. A second data logger was placed outside the carton. All four cartons were packed together in one big box along with one extra pack marked “LAB”. Similarly one TRIX8 LogTag recorder was placed inside and one outside this big box. The full package was then returned to the cold room (2–8 °C).

Products were kept for one month at each location in the country (central store, regional store and service point). No special arrangements were made for storage of the product; storage facilities followed their routine practice. Dispatch of products from central to regional stores and to service points were done by truck. The TRIX8 LogTag recorders that were placed outside the packages were removed at each location and placed in the room where the cold storage (or refrigerator) was located. The ambient temperatures were monitored through these devices. At the end of the storage period in each level, the package containing packs for the lower level was further dispatched and the pack marked LAB was sent to a laboratory in Accra, Ghana (Center for Pharmaceutical Advancement & Training laboratory - CePAT, ISO 17025 accredited) for quality testing. These shipments were done by using messenger bags designed to transport and maintain temperature-sensitive products for 24 h. Temperatures inside the bag were monitored by Q-Tag2 plus (irreversible electronic temperature indicator used to monitor shipment of perishable goods). The study flow is shown in Fig. 1.

Representatives from central, regional and service levels met for a 2-day training on study methodology and roles and responsibilities in handling the study samples. The laboratory personnel were also trained on how to read the VVMs.

At the laboratory, the quality of the initial oxytocin sample (10 ampoules) from the manufacturer and the 13 oxytocin samples (130 ampoules) received from the central store, four regions and eight health centres were evaluated/assessed by staff specifically trained in the study's protocol, using the monograph for Oxytocin Injection specified in the International Pharmacopeia, online version [11]. Oxytocin ampoules were tested for identity, assay, related substances and PH (Table 1). In addition, VVM14 and VVM30 accompanying the samples were read by spectrodensitometer.

The TRIX8 LogTag recorders received at the laboratory were forwarded to WHO, Geneva where the temperature data was retrieved. Temperature data was merged to create temperature profiles in the supply chain for each location.

3. Results

The study was run from March to June 2015. Starting with the dispatch by the manufacturer and concluding at the end of one month's storage period at the service point, full storage/transit period of the supplies ranged from 117 days 22 h 10 min (in Katanga) to 121 days 11 h and 50 min (in Wa). The temperature profile inside the boxes ranged from −9.9 °C (Upper West regional store) to +30.1 °C (Dawia service point). The temperature profile (measured inside the study packs) of the supply chain for each location is given in Table 2. Outside temperatures throughout the study varied between 2.2 °C and 38.9 °C.

Fig. 2 shows minimum and maximum temperature recordings inside the packs along the supply chain throughout the study.

In terms of high and low extremes, it is worth displaying the details of three routes (Dawia and Mpohor for high and Wa for low).

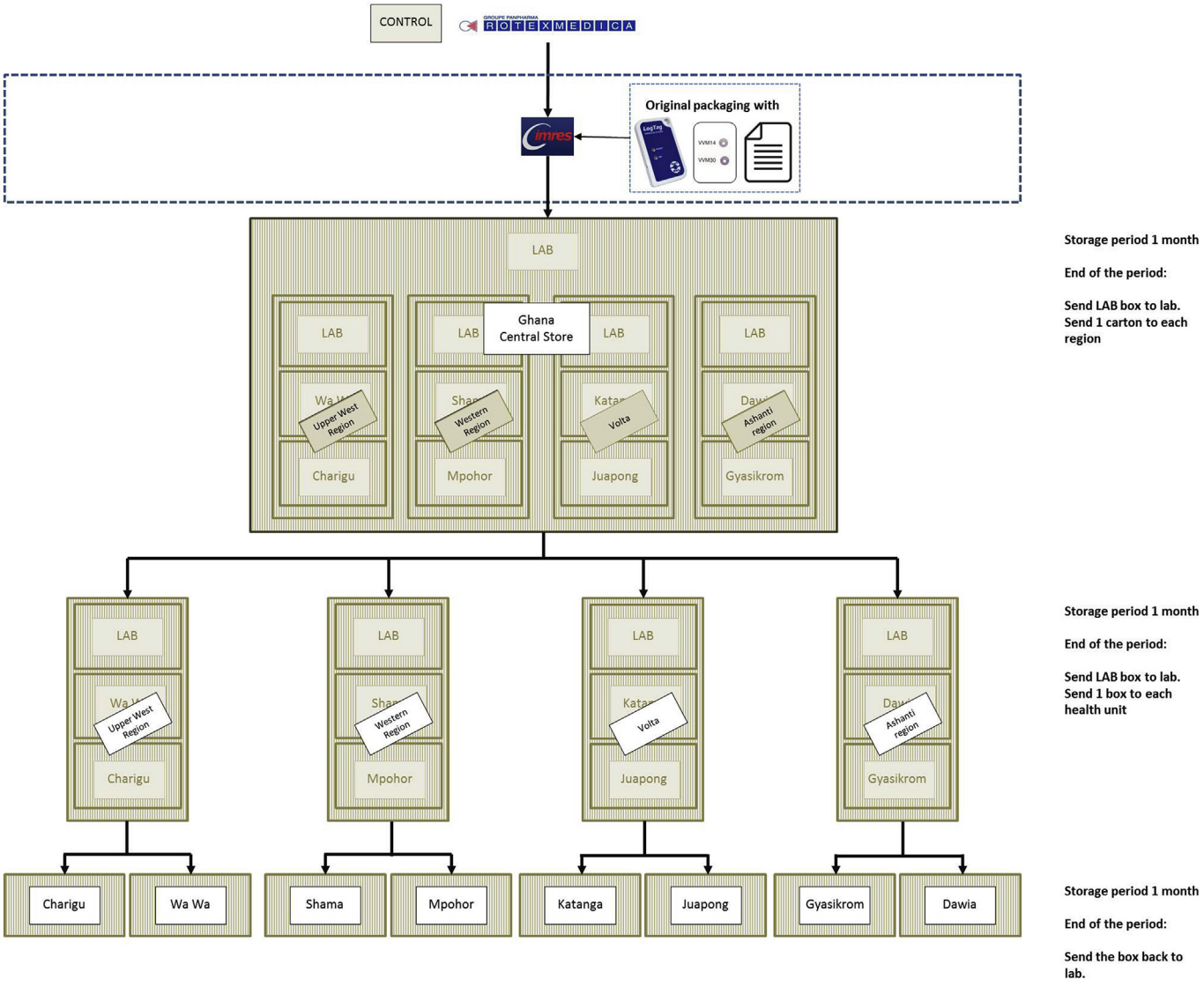

Fig. 1. The study flow.

Table 1
Acceptance criteria for physico-chemical examination of samples according to International Pharmacopeia.

No.	Test	Acceptance criterion
1	Description	A clear, colorless liquid
2	Identification Test B (by HPLC)	The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.
3	PH of injection	3.0–5.0
4	Related substances	In the chromatogram obtained with solution, the area of not more than one peak, other than the principal peak, is greater than the area of the principal peak obtained with solution (2%). No such peak, other than the principal peak, is greater than 2.5 times the area of the principal peak obtained with solution (5%)
5	Assay (by HPLC)	90.0%–110.0% of oxytocin

Fig. 6 displays information on percentage distribution of temperature ranges by all facilities. In general, temperatures were kept within the recommended 2–8 °C range until the products were taken by the primary (central) store. In central store, products were exposed to temperatures above 8 °C for only 1.5% of the storage time. Starting with dispatch of the product to the regional stores, products started to be exposed to temperatures below 2 °C and above 8 °C more frequently. The highest amount of time for exposure to temperatures below 2 °C was observed in Wa and Juapong service points as well as Ashanti and Volta regional stores. Products were exposed to negative temperatures more than 70% of the time in Ashanti regional store and more than 60% of the time in Wa service point. The highest temperature exposures were seen in Dawia, Gyasikrom and Katanga service points as well as in the Western regional store.

The temperature exposure during the shipment from all locations to the laboratory is given in Table 3.

The VVM14 and VVM30 that accompanied each study pack were

Table 2
Temperature profiles along the supply chain of oxytocin from manufacturer to service points in Ghana.

Region	Service point	Temp °C	Transport to IMRES[a]	IMRES store	Transport to Ghana	Transit in airport	Central store	Transport to region	Regional store	Transport to service point	Service point
Western	Shama	Min	2.2	3.3	1.7	2.7	2.9	−8.7	−0.1	2.8	0.1
		Max	15.3 [6.6]	6.6	5.7	5.9	13.8	3.2	24.2	12.0	21.1
	Mpohor	Min	2.2	3.3	1.7	2.7	2.9	−8.7	−0.1	−6.1	−6.1
		Max	15.3 [6.6]	6.6	5.7	5.9	13.8	3.2	24.2	8.6	26.9
Volta	Katanga	Min	2.2	3.3	1.7	2.7	4.1	−6.5	−4.8	−6.9	−1.4
		Max	15.3 [6.6]	6.6	5.7	5.9	12.5	14.0	21.3	13.2	11.3
	Juapong	Min	2.2	3.3	1.7	2.7	4.1	−6.5	−4.8	−1.1	−1.1
		Max	15.3 [6.6]	6.6	5.7	5.9	12.5	14.0	21.3	6.3	16.7
Ashanti	Dawia	Min	2.2	3.3	1.7	2.7	1.9	7.2	−6.7	1.6	0.0
		Max	15.3 [6.6]	6.6	5.7	5.9	13.3	7.5	28.3	9.1	30.1
	Gyasikrom	Min	2.2	3.3	1.7	2.7	1.9	7.2	−6.7	−6.0	−2.3
		Max	15.3 [6.6]	6.6	5.7	5.9	13.3	7.2	28.3	9.8	25.4
Upper West	Charigu	Min	2.2	3.3	1.7	2.7	3.7	1.5	−9.9	4.6	1.2
		Max	15.3 [6.6]	6.6	5.7	5.9	11.5	8.0	9.3	5.1	10.0
	Wa	Min	2.2	3.3	1.7	2.7	3.7	1.5	−9.9	4.8	−7.3
		Max	15.3 [6.6]	6.6	5.7	5.9	11.5	8.0	9.3	10.8	24.0

[a] Figures in parenthesis indicate the highest temperature following conditioning of the recording device. Otherwise temperatures outside brackets correspond to highest temperature without conditioning.

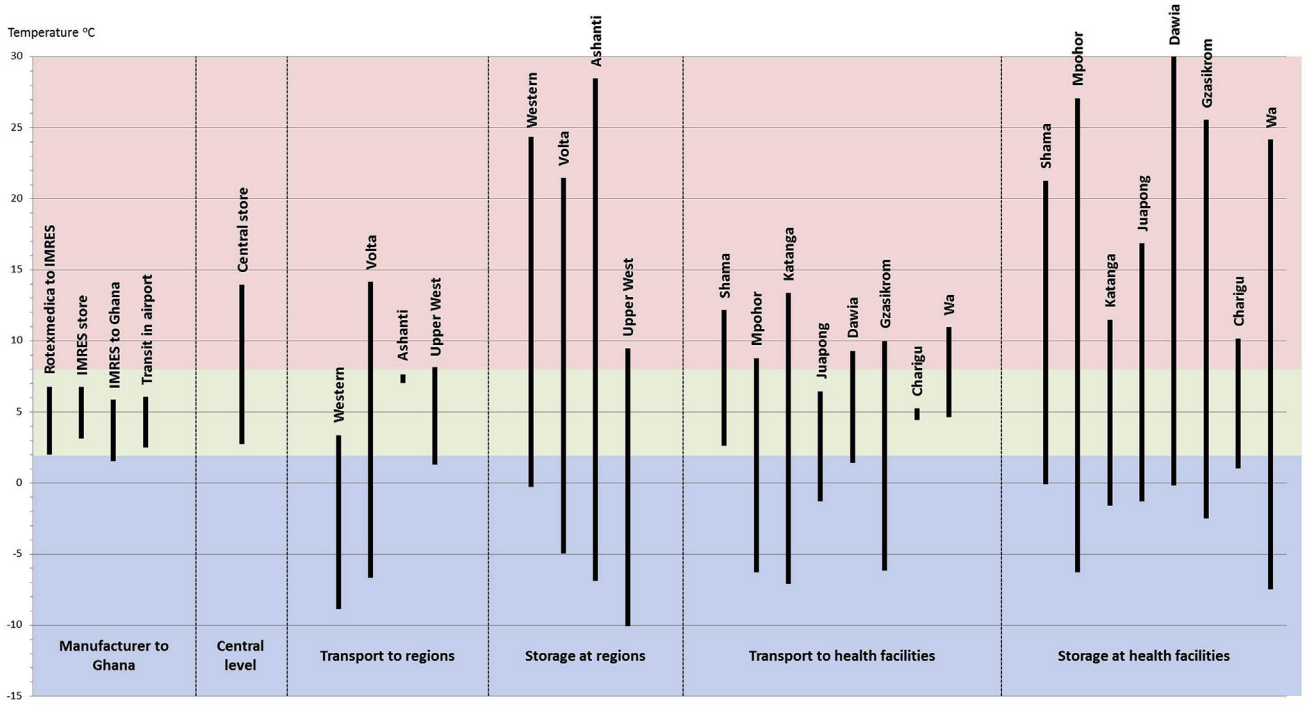

Fig. 2. Minimum and maximum temperature recordings along the supply chain throughout the study.

read by the laboratory (Table 4). The VVM readings were found to be in correlation with the temperature exposure data. The most affected VVM14 and VVM30 were found in Dawia and Mpohor, where the highest and longest temperature excursions occurred (Figs. 3 and 4).

The oxytocin ampoules stored at different levels of the supply chain were tested for appearance, identity, assay, PH value and related substances according to the International Pharmacopeia monograph. The 13 samples of oxytocin tested fully complied with the specifications (Table 5). No significant changes in assay, pH or related substances were detected in any samples compared to the control sample received from the manufacturer. The maximum decrease of assay observed was <2.0% across all levels of the supply chain.

4. Discussion and conclusion

We found that oxytocin samples were kept within the recommended temperature range (2–8 °C) up to reaching the central storage in Ghana. From then on, temperature exposures ranged from −9.9 °C to +30.1 °C. Despite these important deviations in temperature that occurred in Ghana, all 13 samples analyzed were within the required specifications by the International Pharmacopeia.

The study findings are in line with a stability study that was run during the same period, with the same oxytocin batch and at the same laboratory as for the field study. The stability study showed that oxytocin ampoules remained within the required specifications when storing them for three months at 30°C/75% relative

Table 3
Temperature exposure during the shipment of study packs to laboratory.

Location	Duration hh:mm	Min temp	Max temp	High alarm	Low alarm Time (hh:mm)
Central	08:44	2.5	5	–	–
Western	04:51	9.2	11.4	–	–
Shama	75:16	−0.3	18.0	–	–
Mpohor	Unknown[a]	15.1	27.7	–	–
Volta	03:20	1.7	5.8	–	–
Katanga	33:04	−1.9	16.3	–	Yes (13:02)
Juapong	32:22	−3.6	15.2	–	Yes (10:03)
Ashanti	04:35	11.4	15.0	–	–
Dawia	69:50	−1.5	21.4	–	Yes (51:57)
Gyasikrom	79:05	−1.9	31.5	–	–
Upper West	194:04	−0.9	32.9	–	Yes (144:22)
Charigu	Unknown[a]	27.1	33.7	Yes (12:45)	–
Wa	Device was not included				

[a] These devices were not stopped by the laboratory on arrival and continued to record temperatures for 20 days.

Table 4
VVM readings of each supply chain route.

Location	VVM14 R-I		VVM30 R-I	
	Before	After	Before	After
Central	0.35	0.34	0. 42	0.42
Western	0.34	0.33	0.43	0.43
Shama	Not included*			
Mpohor	0.35	0.26	0.43	0. 40
Volta	0.34	0.34	0.43	0.43
Katanga	Not included*			
Juapong	Not included*			
Ashanti	0.34	0.32	0.43	0.43
Dawia	0.34	0.08	0.43	0.32
Gyasikrom	0.35	0.31	0.43	0.42
Upper West	0.34	0.33	0.43	0.43
Charigu	0.34	0.33	0.43	0.43
Wa	0.35	0.31	0.43	0.42

R-I values refer to difference between average readings of "reference" circle and "indicator" surface. The difference increases with temperature.
**In these locations, no VVM card was found in packages received by the laboratory*

humidity (RH) and 40°C/75% RH, for two weeks at 50°C/75% RH and for one week at 60°C/75% RH.

This is the first study that evaluates the extent of temperature exposure impact along the supply chain on the quality of oxytocin from the manufacturer until the service level. Several other studies have analyzed oxytocin samples collected at periphery level facilities or at central level but none of them could conclude whether the oxytocin quality problems encountered were due to quality

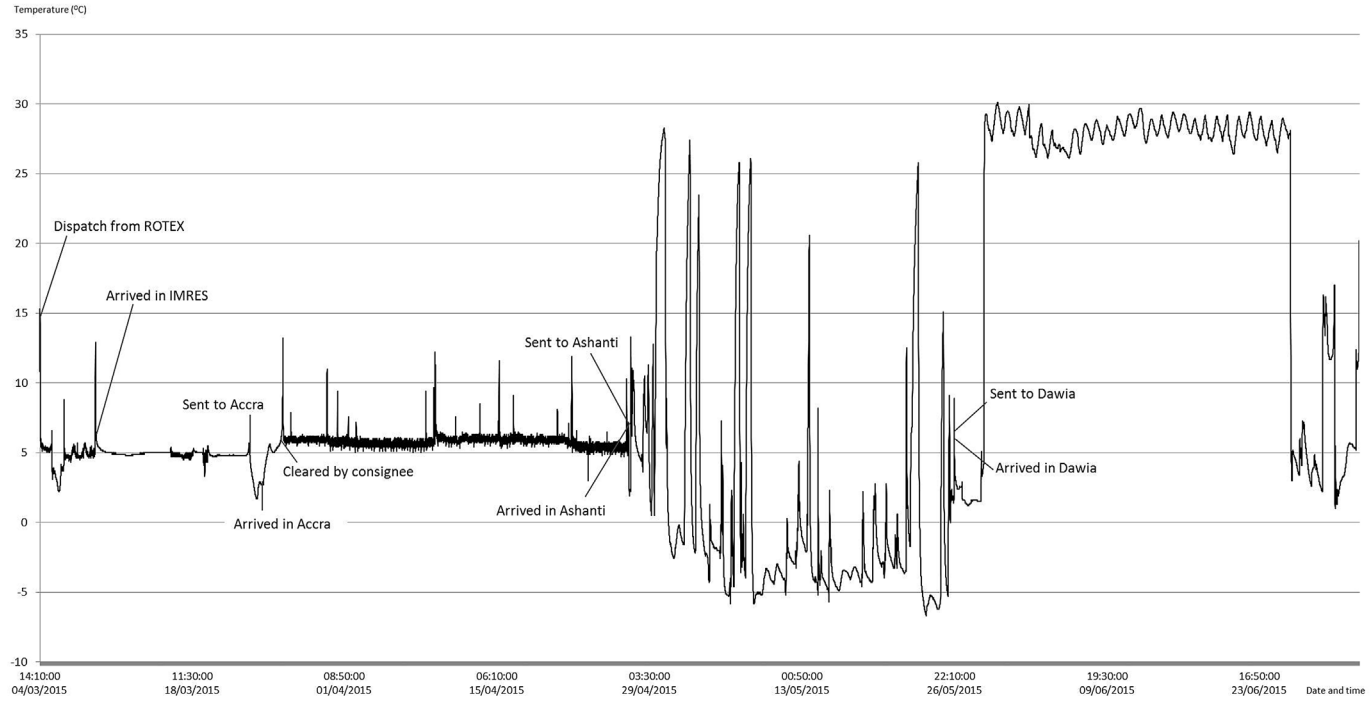

Fig. 3. Temperature profiles throughout the supply chain from manufacturer, Dawia (Ashanthi).

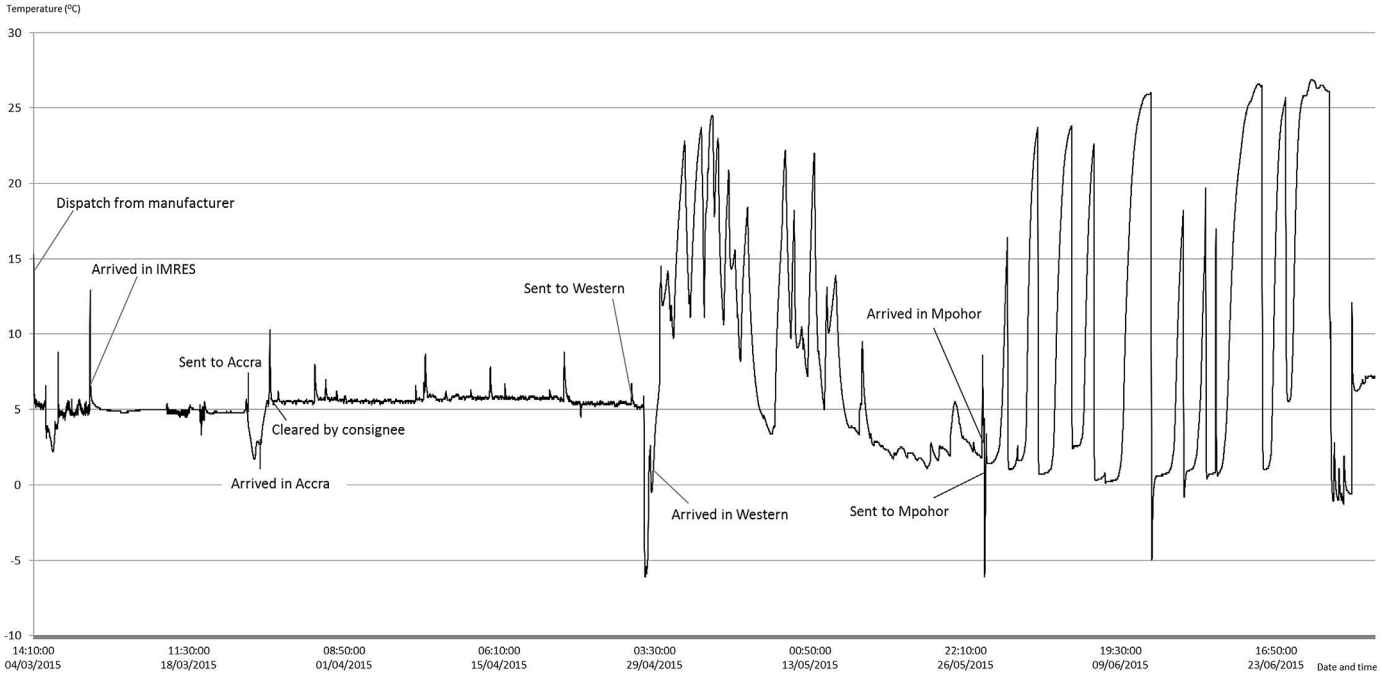

Fig. 4. Temperature profiles throughout the supply chain from manufacturer, Mpohor (Western). Negative temperature exposures were the highest in Volta and Ashanthi regional stores (Figs. 2 and 3) and Wa service point (Fig. 5).

issues at the manufacturer level, or lack of compliance with the storage conditions defined by the manufacturer or a combination of both [6]. In this study we have used a single batch of oxytocin and have tested the quality of this product immediately after it left the manufacturer's facility and then evaluated it again every time the product has been transferred to the next level of the supply chain. We also recorded the temperature and time exposure of the product during the entire supply chain and associate it with the concentration of the product's active ingredient. By using only one oxytocin batch and confirming the good quality at the manufacturer level we were able to discard one factor that could have possibly affected the quality of oxytocin at service level and therefore focused only on the temperature exposures.

For this study, the recommended oxytocin storage conditions were 2–8 °C, but this was not followed 100% of the time. The [cold] supply chain had serious issues both with high and low

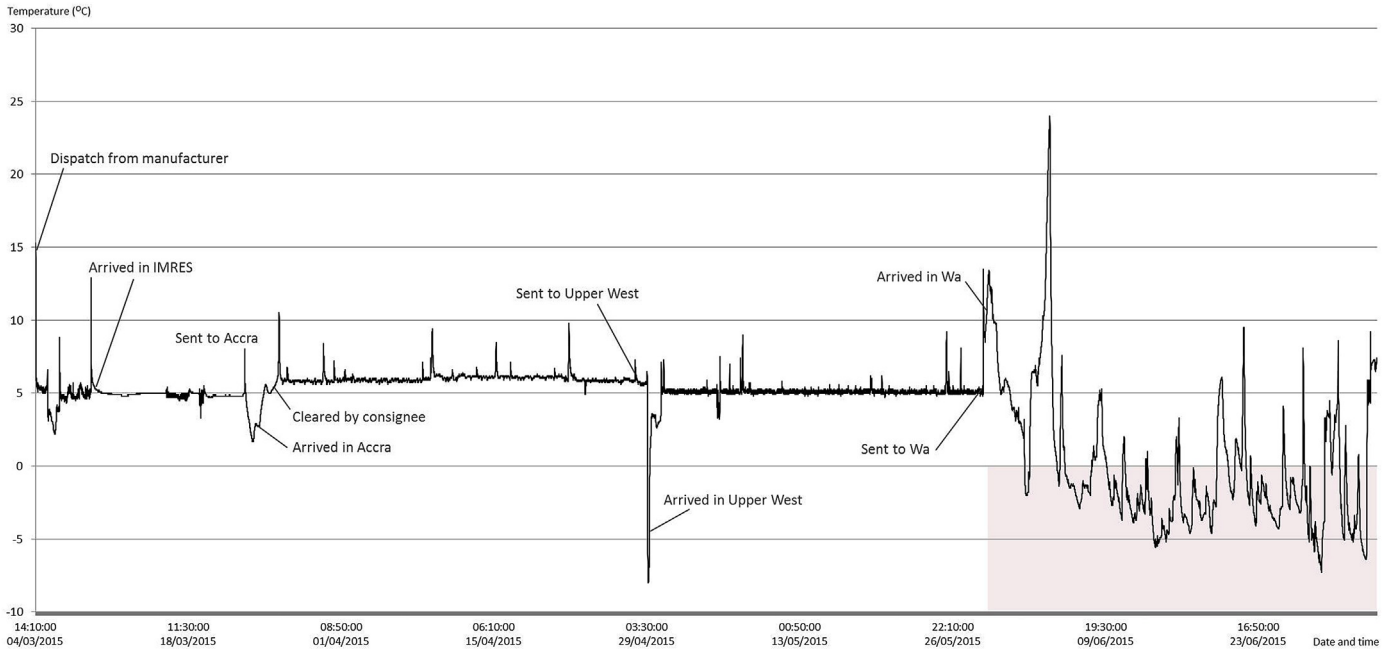

Fig. 5. Temperature profiles throughout the supply chain from manufacturer, Wa (Upper West).

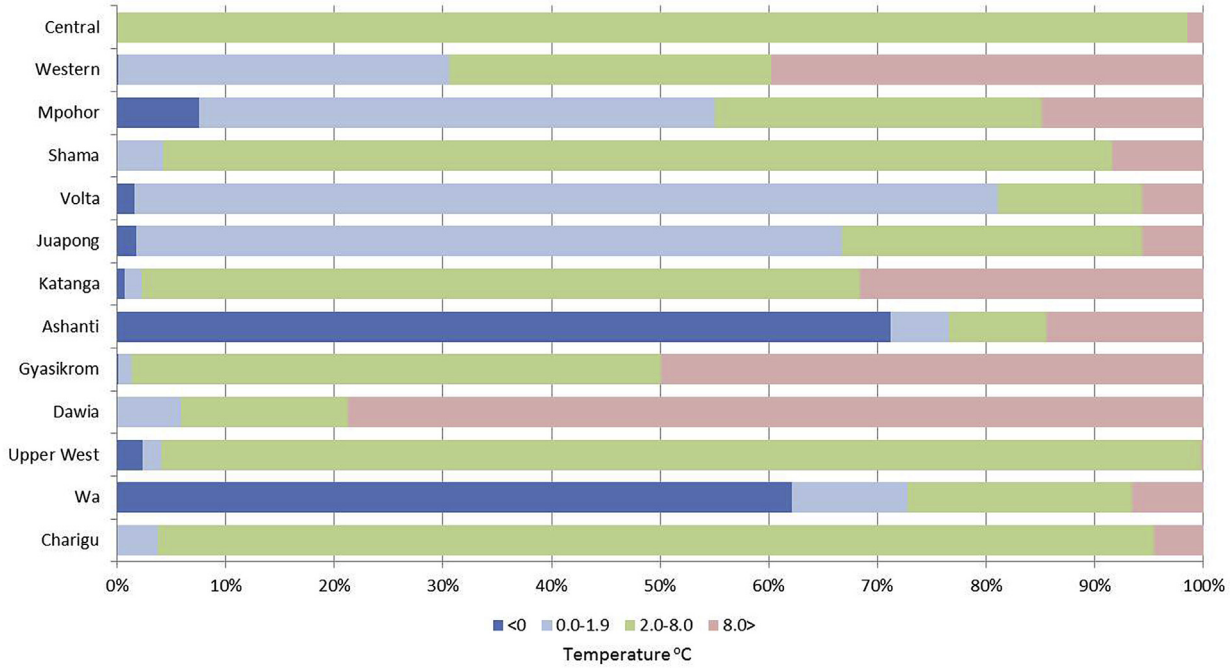

Fig. 6. Percentage distribution of temperature recordings by central, regional and service points (recorded only in indicated facility).

temperature exposures at all levels. The temperature exposures ranged from −9.9 °C to +30.1 °C and occurred at regional level, in transit from regions to service level and at service levels over 30% of the time. However, this did not have any negative impact on the quality of oxytocin, probably due to the stability characteristics of the product and the duration of this supply chain. In the case of time and temperature sensitivity, if other products such as vaccines are exposed to similar temperatures, their quality may be compromised [12].

The main limitations of this study were the short storage time at each level of the supply chain, which could very well be significantly longer in clinical practice and the relatively low temperature during the controlled supply chain. However, the timing of storage and dispatches were suggested by the local supply chain officers as the routine practice for oxytocin and concurs with the resupply interval period reported by Mullany et al. [13], which was limited to approximately one month. It could be argued that the storage time in our study was not enough to detect significant degradation of the oxytocin active ingredient within this particular product, although sensitivity of oxytocin products to these fluctuations in temperature could vary from manufacturer to manufacturer. Even though within this study for this particular oxytocin no

Table 5
Results of physico-chemical parameters by laboratory.

Date Received	Sample/Source	Description & ID	PH	Assay (%)	Related Substances (%)			Conclusion
					SHI @ 2% & 5%	Sum of others	Total Imp.*	
02 APR	From manufacturer	Complies	4.05	103.9	0.35	0.75	1.1	Pass
Regional stores samples								
27 APR	Central	Complies	4.06	103.7	0.39	0.61	1.0	Pass
29 MAY	Western	Complies	4.03	102.7	0.34	0.66	1.0	Pass
28 MAY	Volta	Complies	4.02	102.6	0.39	0.61	1.0	Pass
03 JUN	Ashanti	Complies	4.05	102.5	0.35	0.85	1.2	Pass
03 JUN	Upper West	Complies	4.03	102.2	0.34	0.66	1.0	Pass
Health centres samples								
03 JUL	Shama	Complies	4.09	104.2	0.32	0.38	0.7	Pass
03 JUL	Mpohor	Complies	4.10	103.7	0.34	0.46	0.8	Pass
30 JUN	Katanga	Complies	4.07	103.7	0.32	0.58	0.6	Pass
30 JUN	Juapong	Complies	4.07	103.8	0.36	0.54	0.9	Pass
02 JUL	Dawia	Complies	4.08	103.6	0.51	0.09	0.6	Pass
02 JUL	Gyasikrom	Complies	4.08	104.3	0.32	0.48	0.8	Pass
06 JUL	Charigu	Complies	4.17	102.9	0.36	0.34	0.7	Pass
06 JUL	Wa	Complies	4.07	102.9	0.34	0.36	0.7	Pass

* Total impurity - for information and trending purposes only.

detrimental effects in quality were observed, by developing a better understanding of how different oxytocin products from different sources react to temperature stress, the maternal health community would gain additional insight on how temperature fluctuations and duration may impact the quality of the product in a more general sense. Another limitation could be argued for using the International Pharmacopeia and not the Pharmacopeia followed by the manufacturer. We decided to follow the International Pharmacopeia because in the survey of the quality of medicines identified by the UNCoLSC the quality of oxytocin was assayed following the international pharmacopeia. As this survey influenced our decision at the moment of choosing the oxytocin product and because we wanted to apply the same protocol in several countries, we believed that the best way to compare the quality of different oxytocin products was by applying the International Pharmacopeia.

The results of this study highlight the need for routine oxytocin surveillance and monitored storage conditions along the supply chain. Just offering a product of good quality to the market is not enough. The product's quality must be maintained throughout its life until it is consumed [7] and a way of ensuring this is by following the storage conditions that appear on the label of the product. This should be considered an important part of the strategy to ensure that high quality oxytocin is available to women for the prevention and treatment of postpartum haemorrhage.

Disclosure of interests

None declared.

Ethics approval

This study was exempted from ethical clearance by WHO Ethics Review Committee given that it does not involve human participants according to definition outlined in the WHO ERC Rules of Procedure (ERC.0002870).

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