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Procurement and Supply Management

Ensuring the Availability of Quality Assured Uterotonics in Mozambique

Analysis of Supply Chain Risks associated with Oxytocin Injection

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The USAID Global Health Supply Chain Program-Procurement and Supply Management (GHSC-PSM) project is funded under USAID Contract No. AID-OAA-I-15-0004. GHSC-PSM connects technical solutions and proven commercial processes to promote efficient and cost-effective health supply chains worldwide. Our goal is to ensure uninterrupted supplies of health commodities to save lives and create a healthier future for all. The project purchases and delivers health commodities, offers comprehensive technical assistance to strengthen national supply chain systems, and provides global supply chain leadership.

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Acronyms

C	Celsius
CMAM	Central Medical Stores
DNF	National Pharmacy Directorate
GHSC-PSM	USAID Global Health Supply Chain Program-Procurement and Supply Management
IU	international unit
LMICs	low- and middle-income countries
MNCH	maternal, newborn, and child health
PPH	post-partum hemorrhage
PQM	Promoting Quality of Medicines
TO4	Task Order 4
UNICEF	United Nations Children's Fund
UNFPA	United Nations Population Fund
WHO	World Health Organization

Executive Summary

Post-partum hemorrhage (PPH) – or excessive bleeding after childbirth – is a leading cause of maternal mortality globally and in Mozambique[1]. PPH is preventable and treatable with inexpensive medicines that are widely available[2]. According to the World Health Organization (WHO) recommendations, oxytocin is a preferred medicine for prevention and treatment of PPH, and the majority of low- and middle-income countries (LMICs) include oxytocin as first line in standard treatment guidelines and as an essential medicine. In Mozambique, a 2018 study reported that 25 out of 135 (about 15%) oxytocin samples were substandard in terms of manufacturing, storage, and distribution[3]. These test failures highlight that there is a quantifiable amount of poor-quality oxytocin injection in circulation in Mozambique.

The objective of this activity was to assess Mozambique's public sector supply chain to identify high risk practices that may compromise oxytocin quality and develop a set of context-specific options that Mozambique's Ministry of Health may consider to safeguard uterotonic quality up to the point of administration to the patient. This assessment used a mixed method approach—analysis of logistics data, temperature data, oxytocin stability data, and policy document review—to analyze, model real condition degradation, and document findings related to oxytocin quality.

The assessment found that ambient storage of oxytocin in Mozambique is a high-risk practice that will likely contribute to the presence of poor-quality oxytocin at the point of use. Typically, oxytocin may spend up to two years in the supply chain, which can contribute to substantial cumulative exposure to higher than acceptable temperatures when not refrigerated. In Mozambique, oxytocin will either come through a standard push/pull model called "via classica" or it is included in essential medicines kits "Kits US". Kitted oxytocin is typically labelled for storage outside of the refrigerator (either below 25 or 30 degrees Celsius[C]). Via classica oxytocin when labeled 2-8°C is usually kept under refrigeration whereas kitted and 25-30°C labeled oxytocin is stored in ambient conditions is likely exposed to high temperatures at storage locations and during transportation. The analysis showed that when oxytocin is exposed to supply chain conditions in Mozambique, the amount of oxytocin API present is either very or below the acceptable range. Summary recommended considerations are further detailed.

Ensure that only quality-assured, appropriately labelled oxytocin is registered, waivered, procured, and distributed. Product labelling guides supply chain and facility manager storage practices. Oxytocin that is consistently labelled for storage between 2-8 degrees C will prevent confusion and help ensure appropriate storage.

Consider removing oxytocin from essential medicines kits and where appropriate, replace it with oral misoprostol for PPH. In Mozambique, ambient storage may result in the presence of poor-quality oxytocin at the point of use. Misoprostol for PPH may be stored in ambient conditions and is appropriate for use in community settings (i.e., does not require injection). Replacement of oxytocin with misoprostol for PPH would be appropriate due to these characteristics and would reduce the need for oxytocin and required cold chain infrastructure.

Ensure that via classica oxytocin is stored in cold storage, irrespective of labelling. Effective communication on this point should be employed to help raise awareness and clarify any confusion. This recommendation would align with WHO/UNFPA/UNICEF guidance on the storage and management of oxytocin.[4] Other countries—Ghana, Liberia, and Uganda—have issued memos to clarify oxytocin storage requirements. Mozambique may want to consider a similar action to help clarify any confusion on oxytocin storage requirements.

Reconsider shipment schedule and amount of time spent at each warehouse level. If Mozambique were to change from an annual shipment/delivery schedule to accommodate quarterly ordering and distribution, time spent in the supply chain would be significantly. This would substantively reduce the cumulative time-temperature exposure and associated degradation risk.

During international and domestic shipment and transportation, oxytocin should always be stored in cold storage, e.g., in refrigerated containers, refrigerated trucks, and/or in cold boxes with ice. Transportation—including international ocean shipment and in-country transportation by truck—are the most significant risk points for oxytocin. Ocean shipment can take several months, and if oxytocin is not shipped in a refrigerated container, it will likely be exposed to higher that acceptable temperatures for a long duration. Interior truck temperatures can get extremely high, which results in rapid product degradation. During transport, oxytocin should always be kept under refrigeration or in cold boxes with ice.

Consider pairing uterotonic options with tranexamic acid to treat PPH. Updated WHO recommendations on the use of tranexamic acid for PPH treatment may be worth considering. Tranexamic acid is administered intravenously and does not require cold storage. When administered in conjunction with uterotonics, it decreases the risk of death due to PPH.

Adoption of these consideration will help ensure the quality of uterotonics, and ultimately, will help save maternal lives.

Context and Background

Maternal mortality in Mozambique

Mozambique has made significant progress towards improving access to maternal health services since 2000. However, as of 2015, maternal mortality was still unacceptably high at 489 deaths per 100,000 live births[5], indicating that there is room to improve the quality of maternal health services, including the quality of medicines used for maternal care. Post-partum hemorrhage (PPH) – or excessive bleeding after childbirth – is a leading cause of maternal mortality[1]. Reducing PPH related deaths is a critical to improve maternal health outcomes in Mozambique.

Oxytocin quality challenges

PPH is preventable and treatable with inexpensive medicines that are widely available[2]. According to WHO recommendations, oxytocin is a preferred medicine for prevention and treatment of PPH, and the majority of LMICs include oxytocin as first line in standard treatment guidelines and as an essential medicine. Oxytocin's effectiveness is widely recognized[6,7]; however, the presence of substandard oxytocin in low- and middle-income countries (LMICs) is well-documented. A 2016 systematic review reported widespread oxytocin that did not meet quality assurance standards[8]. A 2020 systematic review on the quality of maternal health products reported high assay failure rates for oxytocin, ergometrine, and misoprostol at 39.7 percent, 75.4 percent, and 38.7 percent, respectively[9]. In Mozambique, a 2018 study reported that 25 out of 135 (about 15%) oxytocin samples were substandard in terms of manufacturing, storage, and distribution[3]. These test failures highlight that there is a measurable amount of poor-quality oxytocin injection in circulation in Mozambique.

Oxytocin quality deficiencies may occur at the point of manufacturer and/or due to excessive exposure to higher than acceptable temperatures. In 2019, WHO, the United Nations Population Fund (UNFPA), and the United Nations Children's Fund (UNICEF) released a joint-statement that clarifies storage requirements for oxytocin, stating that oxytocin should be labeled for storage between 2-8° Celsius (C) and managed in a cold chain of 2-8° C for storage and distribution[4]. While this statement clearly states that oxytocin should remain in cold storage throughout the supply chain, confusion among stakeholders in LMICs continues, and oxytocin is often stored and transported in hot, ambient conditions. In Mozambique, oxytocin may be procured as a part of a general essential medicines kit – and when this happens, oxytocin is stored in ambient, non-temperature-controlled environments. Use of poor-quality oxytocin may result in additional interventions, including administration of additional uterotonics to

prevent PPH and a range of surgical, medical and manual interventions to treat PPH. In cases where these interventions are unsuccessful, death may occur.

Additional uterotonic options

From 2017-2020, new advances in PPH management-related products have prompted WHO to revisit and revise PPH-related treatment recommendations. In 2017 and 2018, two major studies – the WOMAN trial and the CHAMPION trial – were published[10,11]. In the WOMAN trial, researchers demonstrated that tranexamic acid, an antifibrinolytic used to treat heavy bleeding, reduces death due to bleeding in women with PPH with no adverse effects[11]. The CHAMPION trial compared the effectiveness of a novel, heat stable formulation of carbetocin to oxytocin for preventing PPH and demonstrated that the new product is as effective as oxytocin[10]. In response, WHO released new and revised recommendations. Summary changes include:

- Tranexamic acid recommendations were updated to include use of tranexamic acid in all cases of PPH rather than when uterotonics had failed to stop bleeding[12].
- Heat stable carbetocin was added to WHO's PPH prevention guidelines for the first time for prevention of PPH; notably, it is not indicated for treatment[13].
- Additional clarity was provided on the use of misoprostol for PPH prevention, including specificity around misoprostol's application in settings where skilled providers trained to administer injectable uterotonic may not be present and/or cold chain may not be available[13].
- Where multiple uterotonic options are available and in settings where cold chain and trained health care providers are present , WHO recommends that oxytocin in 10 international units (IU) be used[13].

These changes effectively provide countries with a suite of PPH management options to choose from depending on context and availability, such as the ability to guarantee end-to-end cold chain and the presence of trained health care personnel.

Objectives

The USAID Global Health Supply Chain Program-Procurement and Management (GHSC-PSM) project provides procurement and technical assistance support to strengthen government supply chain systems to ensure health commodity availability at the last mile. Under Task Order 4 (TO4), GHSC-PSM partners with government counterparts to strengthen government systems to procure and manage maternal, newborn, and child health (MNCH) commodities. As part of the TO4 activity portfolio, GHSC-PSM has led several initiatives that support countries to improve the availability of quality-assured uterotonics, including country-led efforts to identify supply chain constraints that compromise oxytocin quality and develop tailored strategies to address barriers and constraints.

Given known oxytocin quality issues in Mozambique and using lessons learned from similar activities in other LMICs, the objective of this activity was twofold, including to:

- Assess Mozambique's public sector supply chain to identify high risk practices that may compromise oxytocin quality
- Develop a set of context-specific options that Mozambique's Ministry of Health may consider to safeguard uterotonic quality up to the point of administration to the patient

The analysis and options serve to inform government-led decisions on PPH management guidelines, medicine and commodity requirements, and supply chain management strategy and operations.

Summary methodology

Compromised oxytocin quality may result from different causes: poor adherence to current Good Manufacturing Practices and excessive exposure to higher than acceptable temperatures. This activity examined procurement and supply chain management practices that may link to one or both causes. The activity was carried out in three phases, which are described below.

Phase 1. Establish how oxytocin enters and moves through the supply chain from point of manufacture to the point of service delivery

GHSC-PSM analysts reviewed country policy and strategy documents, i.e., standard treatment guidelines, the national essential medicines list, and other strategy-related documents and held discussions with relevant in-country stakeholders. A cursory review of quality related documents was carried out to inform and contextualize the analysis. Mozambique's list of registered oxytocin products and implementing partner reports, including quality testing results from the Promoting Quality Medicines Program (PQM), were consulted. Additional follow up with key informants was carried out as needed.

Phase 2. Determine the duration and severity of temperature exposure throughout

Issues and consumption data from in-country logistics systems – MACs, SIMAM and SIGLUS – were extracted and analyzed to determine product flow and storage duration. Project distribution and route data was analyzed and used to inform transportation estimates. Temperature data for static storage sites was drawn from the IBM PAIRS API and internal GHSC-PSM temperature monitoring data informed transport temperature estimates.

Phase 3. Model oxytocin degradation to elicit major points of risk within the supply chain

An interactive application to model oxytocin degradation over time was built by Monash University for this activity using the R Shiny package in R (version 3.6.1). Data from previous UNFPA-funded accelerated stability studies using oxytocin ampoules were used in the model (published in BMJ Open). The following distribution path was used: ship (from manufacturer to port) > port > transport > central warehouse > transport > provincial warehouse > transport > district warehouse > transport > facility. Data and estimates from phase 2 were populated in the model, and individual routes from point of manufacture to specific health facility sites were modelled to assess risk according to product degradation.

Following the analysis, major risks were identified and options for addressing risks were developed. Further detailed documentation on methods employed is available in Annex A.

Analysis and findings

Oxytocin supply chain and regulatory overview

Procurement

In Mozambique, the Central Medical Stores (CMAM) is charged with procurement and distribution of oxytocin. Oxytocin ampoules are procured and distributed "via classica" or as part of an essential medicines kit "Kit US". Via classica oxytocin, when labeled 2-8°C, is usually kept under refrigeration whereas kitted and 25-30°C labeled oxytocin is stored in ambient conditions is likely exposed to high temperatures at storage locations and during transportation. An estimated 60-75% of ampoules are distributed via classica, and 25-40% ampoules via kits.

CMAM tenders annually to select a domestic or internationally affiliated wholesaler to source and import oxytocin for the public sector. If the oxytocin is part of a kit, typically IDA or MissionPharma are often selected. Selected wholesalers source oxytocin from international manufacturers and suppliers because there is no domestic manufacturing of oxytocin in Mozambique.

Quality assurance and regulation

The National Pharmacy Directorate (DNF) has the mandate to assure the quality of medicines in Mozambique and carries out key regulatory functions, including medicines registration, importation inspection, and post-marketing surveillance. For any imported pharmaceuticals, including oxytocin, the DNF must grant a registration or registration waiver to the selected wholesaler seeking to import the product. Registrations are typically valid for five years. Additionally, registration waivers are commonly granted when non-registered medicines are considered urgent. Interviewees further indicated that products included essential medicines kits may often receive registration waivers as well. As of April 2021, there were 5 registered oxytocin products as depicted in table 1. The complete list of registered oxytocin and misoprostol products are provided in the annex in Portuguese and English.

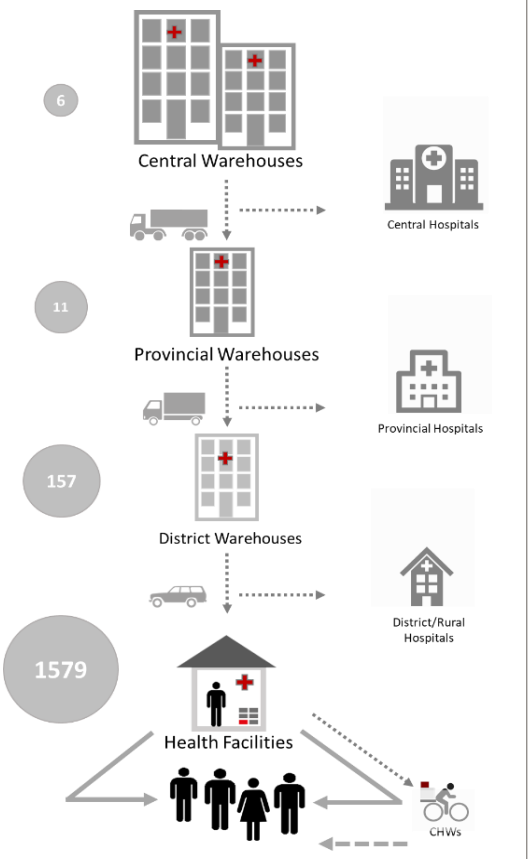
Table 1. Registered oxytocin products and formulations

Generic Name	Dosage	Manufacturer	Authorization Date	Enterprise
Oxytocin	5 IU/mL	Neon Laboratories Ltd - India	18-3-2015	MEDAFRICA, LDA
Oxytocin	5 IU/mL	BKRS Pharma PVT. Ltd - India	18-9-2017	EVEREADY PHARMA LDA

Oxytocin	5 IU/mL	Alchemy Medicine Pvt Ltd - India	12-11-2019	ARTEMIS PHARMACEUTICALS
Oxytocin	10 IU/mL	Alchemy Medicine Pvt Ltd - India	3-12-2019	ARTEMIS PHARMACEUTICALS
Oxytocin	10 IU/mL	Umedica Laboratories Pvt. Ltd - India	24-9-2020	MISSONPHARMA MOZAMBIQUE

The frequent use of waivers may undermine the regulatory process for maintaining quality medicines. A 2018 study examined the quality of oxytocin in Mozambique and of the 135 tested oxytocin samples, 21 were substandard[3]. All the oxytocin samples received registration waivers, and therefore, quality specifications were not assessed[3]. Furthermore, 131 of the 135 samples were labeled for storage under 25 degrees C rather than for storage between 2-8 degrees C[3]. The temperature ranged between 24-27 degrees C when the samples were collected. Of the four samples that were labeled for storage between 2-8 degrees C, all were stored according to the manufacturer's specifications[3].

Figure 1. Mozambique supply chain



Shipment, transportation, and distribution

International shipment

Because CMAM sources oxytocin from international suppliers, it first must be shipped from abroad, which is typically via ocean in 40-foot containers from Asia, Europe, or South America. If via classica oxytocin is labelled for storage between 2-8 degrees C, it is shipped in refrigerated containers; however, kitted oxytocin and oxytocin labelled for storage at below 25 and 30 degrees C are kept under ambient conditions, which can increase the rate of degradation

Arrival at port

Upon arrival at port, all pharmaceuticals, including oxytocin, must be inspected prior to release, and in some cases, clearance may take up to three days. When oxytocin is shipped via classica and kept in refrigerated containers, the additional clearance time

does not impact the quality of the product. However, kitted oxytocin stored in non-temperature-controlled containers is at risk of exposure to high temperatures, especially if it remains in the park for a few days prior to reception at central warehouse locations.

Domestic storage and distribution

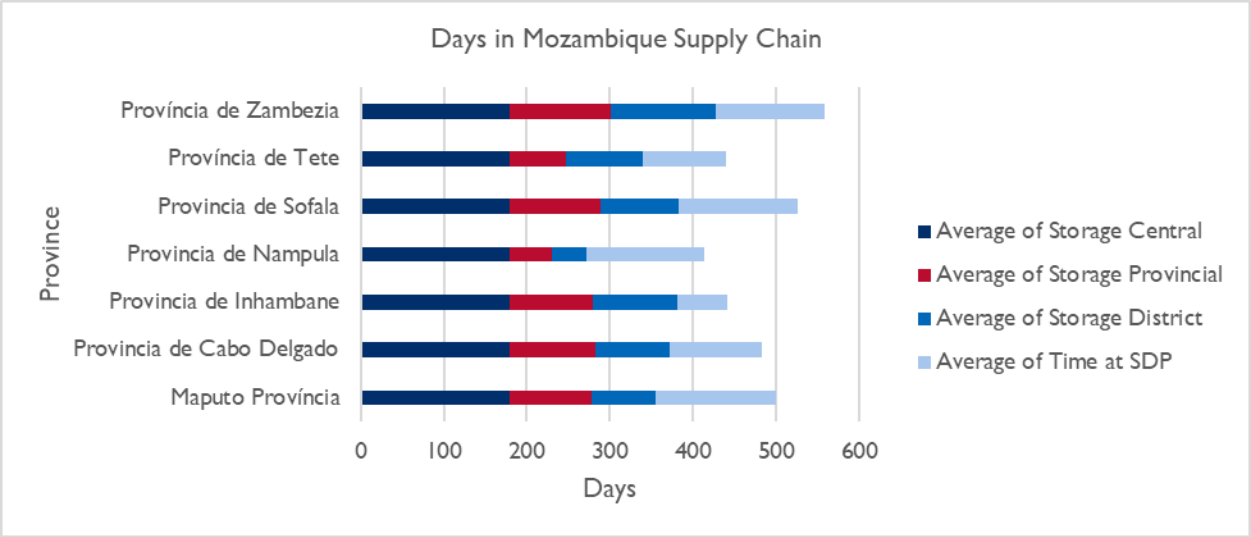
Mozambique's public sector supply is a four-tiered system (Figure 1), and via classica and kitted oxytocin are transported and distributed through these four tiers. Initially, when oxytocin is cleared at port, it is usually transferred directly to each province. However, buffer stock is sent to a central warehouse in either Maputo, Beira, or Nampula where it may remain for up to 180 days. Via classica oxytocin is typically stored in cold storage in the central warehouse; however, kitted oxytocin is stored at room temperature.

CMAM transports oxytocin with other essential medicines to provincial and then district warehouses where it remains for an average of 90 days at each level (a cumulative 180 days). Provincial warehouses have cold storage; however, the availability of refrigerators at district level warehouses is more variable. After district level storage, oxytocin is then distributed to health facilities. Many health facilities do not have dedicated non-vaccine refrigerators to store oxytocin and other temperature sensitive products (e.g., insulin). This study did not look at the availability of vaccine cold storage because the vaccine cold chain is typically run separately from essential medicine supply chains and storing non-vaccine products in vaccine-designated refrigerators in not permitted to maintain vaccine quality. Oxytocin can spend up to an average of 127 days stored at health facilities, and in many cases, is not refrigerated. Furthermore, when oxytocin is sent via a kit, it may end up in a facility that does not provide labor and delivery services or only has a limited set of them, and in these cases, it is sent back to the district level for redistribution. The return and redistribution process can add an additional 90 days of ambient storage to the cumulative duration of storage and heat exposure and is an extremely high-risk practice.

Cumulative time spent in in-country supply chain

Figure 2 illustrates the average amount of time that oxytocin spends at each point from port to the service level. Figure 2 does not account for the previously described return and redistribution of kitted oxytocin. Annex B includes detailed facility level data. Transport times were minimal and are not included in this chart. Average in-country times ranged from less than one day up to two, but transport times greater than one day were rare.

Figure 2. Average number of dates spent in supply chain, by province



On average, oxytocin remains in the Mozambique supply chain for over a year excluding instances where it is returned to the district warehouse and is redistributed.

Ambient temperatures in warehouses, facilities, and trucks

Warehouse and facility GPS coordinates were matches with temperature date from the same coordinates in the IBM PAIRS API. Figure 3 provides summary statistics on the range of temperatures across all included regions at noon over a 12-month period from 2016-2020.

Figure 3. Distribution of noontime temperatures at all included sites (warehouses and health facilities), across all regions, years 2016-2020

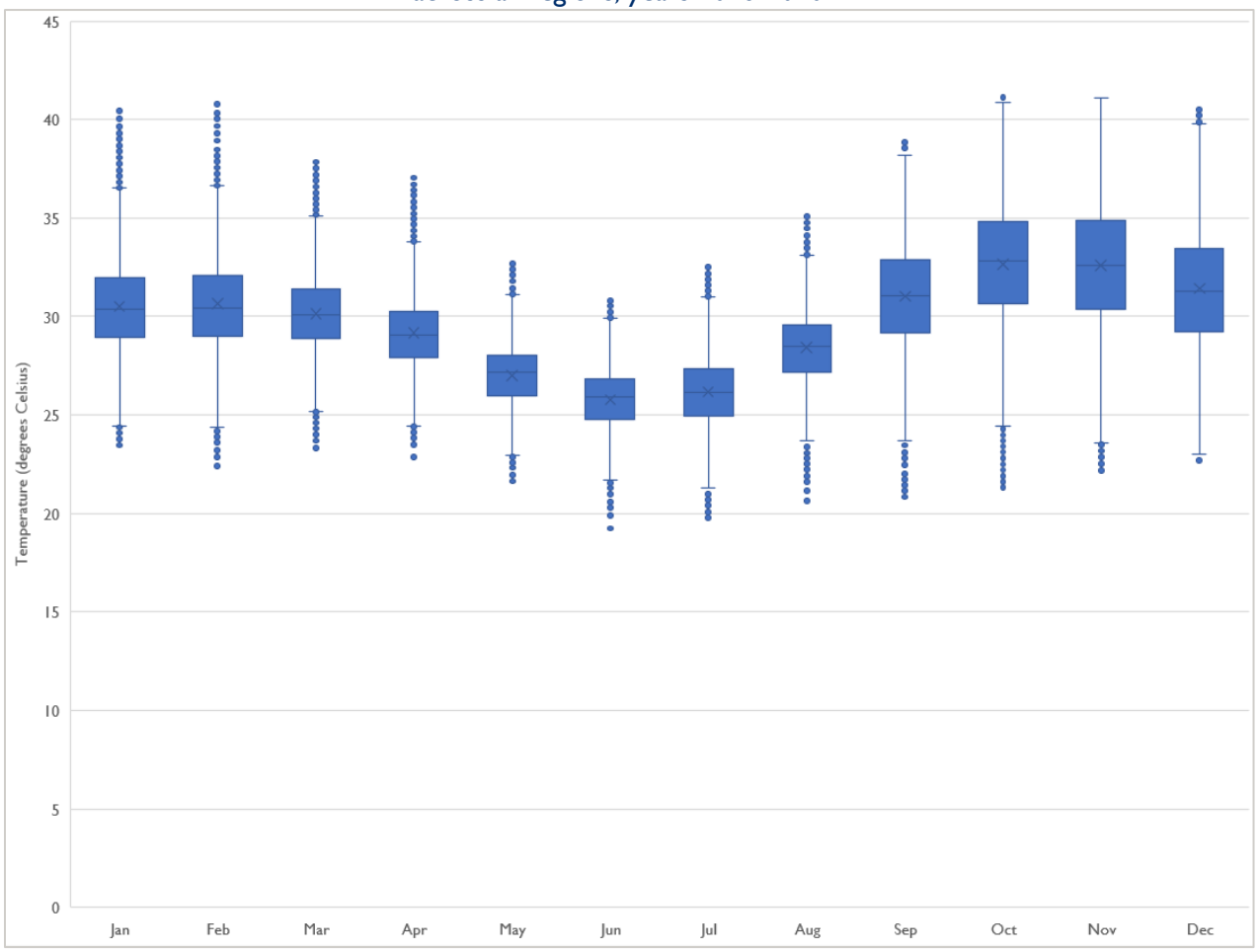
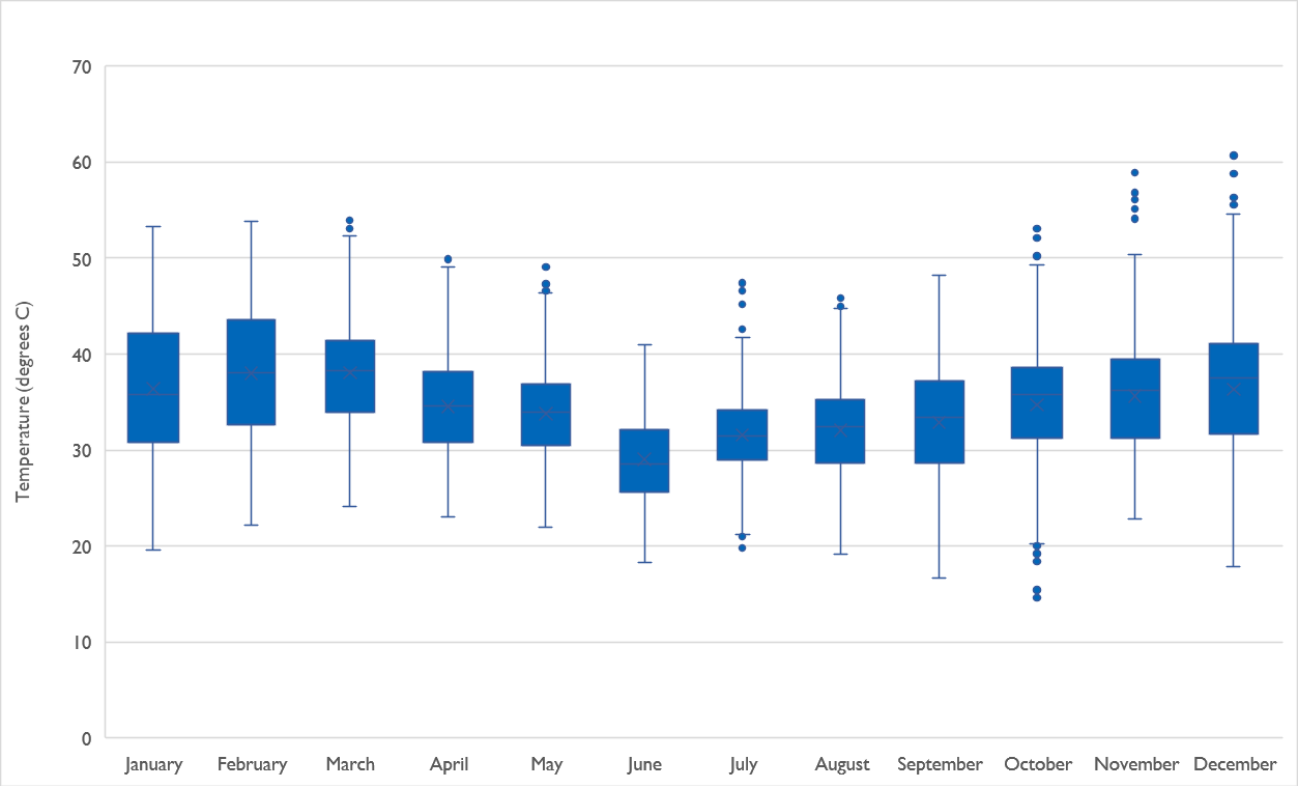


Figure 3 illustrates that midday ambient temperatures in Mozambique are consistently above recommended storage conditions as specified by the manufacturer. These data are further broken down by region in Annex C.

Internal GHSC-PSM truck data confirms that oxytocin not stored in cold storage during in-country transportation may be exposed to excessively high temperatures (Figure 4).

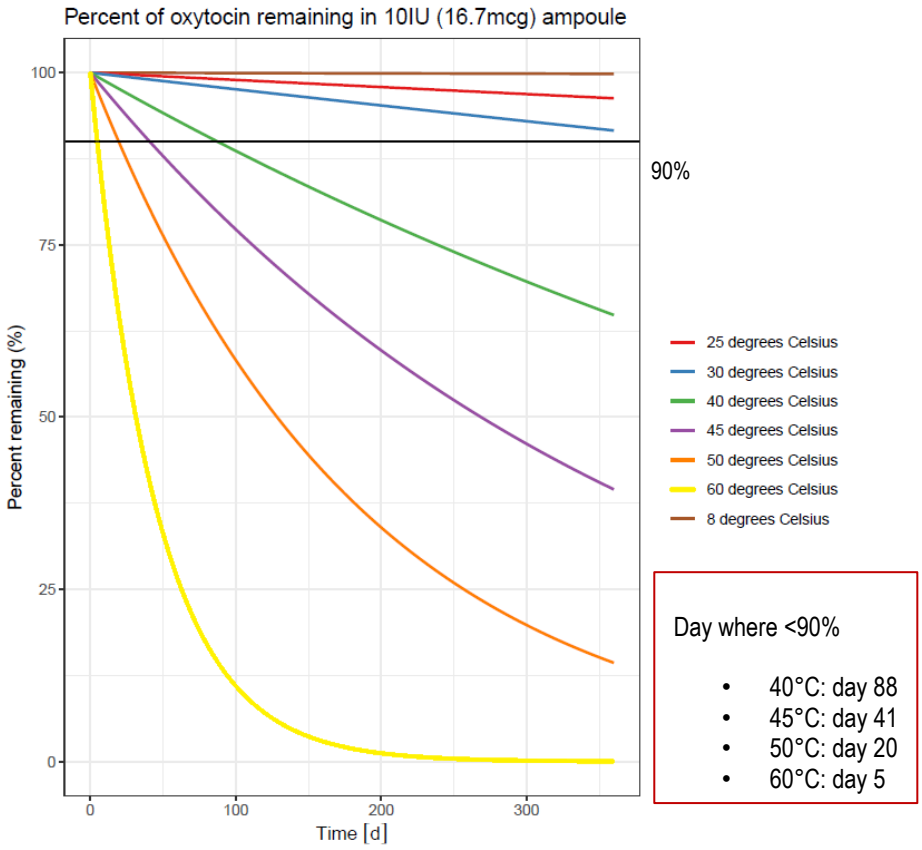
Figure 4. Distribution of internal truck temperatures between 12pm and 1pm across, year 2019



Oxytocin degradation over time at different temperatures

Stability studies have been conducted to understand the effect of elevated temperature storage on the oxytocin content in 10 IU oxytocin ampoules over time (published in part in BMJ open). Figure 5 summarizes the oxytocin remaining in ampoules stored at various temperatures between 8 degrees C (refrigerated storage) and 60 degrees C for 365 days. These data are based on studies of multiple batches of product from several manufacturers. At all temperatures above 30 degrees C, oxytocin content decreases below 90% of the specified content – the internationally recognized standard of quality – in fewer than a 100 days storage.

Figure 5. Oxytocin remaining in ampoules when exposed to different temperatures



Route simulation results

To explore the impact of temperature on the percent of oxytocin remaining in a 10IU (16.7 mcg) ampoule across a supply chain, the longest route with the highest average temperature (Table 2 and Figure 6) was simulated. The time spent at each location and temperature at each location were either obtained directly from analyzed LMIS data or were estimates based on literature values and/or local experience. Distribution of oxytocin via classica (i.e. kept in cold storage) and by kit (i.e. kept at ambient temperature) were simulated for the selected route.

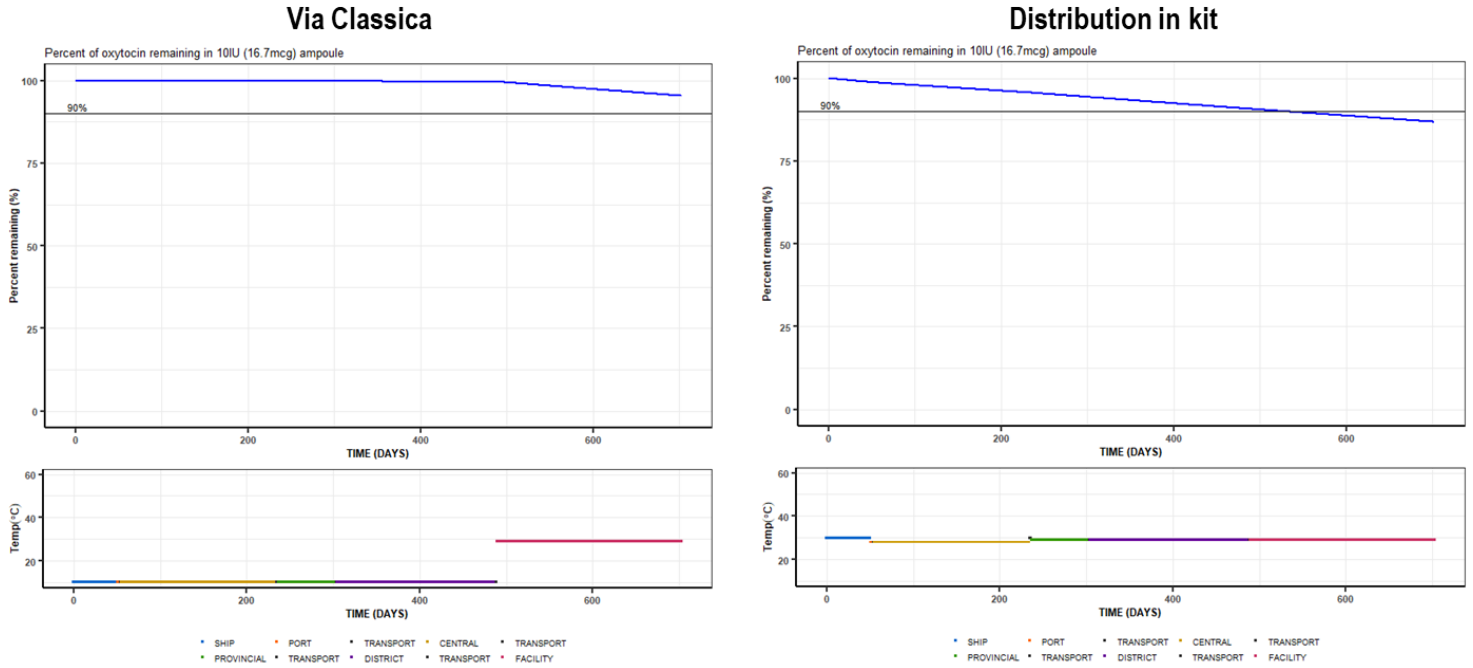
The simulation results are shown in Figure 6. Assuming that via classica oxytocin is kept under refrigeration until it reaches service delivery point level, the percent of oxytocin remains above 90% of the specified content (i.e. 10IU or 16.7 mcg) throughout the duration spent in the supply chain. Whereas when oxytocin is distributed by a kit, the percent of oxytocin is below 90% by the end of the supply chain duration. The model and simulations were translated into an interactive application which allows users to see the impact of temperature and time at location on the percent of oxytocin remaining in real-time (see Annex D).

Table 2. Temperature and time spent at locations along longest supply chain route with the highest average temperature

		Ship	Port	Transport	Central	Transport	Provincial	Transport	District	Transport	Facility
Name		-	Maputo	-	Zimpeto	-	Tete	-	Moatize	-	Benga[B]
Days		50	3	0.02[A]	180	2.5	67	0.5	184	1	214
Temp (°C)	**Kit**	30	28	28	28	30	29	29	29	29	29
	Classica[C]	8	8	8	8	8	8	8	8	8	29

[A] Put as 0.5 days in R Shiny app
[B] No fridge available at this facility
[C] Put as 10°C in R Shiny app

Figure 6. Percent of oxytocin remaining across the longest supply chain route with the highest average temperature when distributed via classica or kit



It was hypothesized that transport via truck from warehouse to warehouse would have a significant impact on the percent of oxytocin remaining, as truck temperatures can vary widely throughout the day particularly in warmer months. Additional analyses were conducted based on temperature data measured at hourly intervals inside trucks used at various points along the supply chain within Mozambique (truck specific data is shown in Annex E). Notably, the route for kit distribution did not model the scenario when health facilities send oxytocin back to district level where it may be redistributed to other health facilities. This last step is extremely high risk as it will result in additional degradation beyond what is modelled in Figure 6. It should be recognized in relation to kit supplies stored at ambient conditions, these data indicate that in all cases the product will likely be exposed to temperatures above that at which the shelf-life is determined by the manufacturer. Therefore, even in cases where the predicted oxytocin content remains above 90% during these simulations, the stated shelf-life can no longer be relied upon as an accurate indicator of the duration of product quality.

When truck transport occurs during cooler seasons (Figure 7), the percent of oxytocin remaining stays above 90% by the end of the supply chain, and the range appears quite narrow. When truck transport occurs during warmer months (Figure 8) the percent of oxytocin remaining range was wider, driven by the maximum temperatures. Although the interquartile range appeared similar regardless of whether transport occurred in warmer or cooler seasons.

Table 3. Temperature and time spent at locations along supply chain route with longest transport durations – supply chain starting in January

		Ship	Port	Transport	Central	Transport	Provincial	Transport	District	Transport	Facility
Name		-	Maputo	-	Zimpeto	-	Niassa	-	de Marrupa	-	Marrupa
Days		50	3	0.02	180	5	77	1	112	1	90[A]
Month		Jan	Feb	Feb	Feb	Aug	Aug	Nov	Nov	Mar[B]	Mar
Truck name		-	-	-	-	Foselev	-	Inhambane DPM	-	Tete Angonia	
Temp (°C)	**Kit**	30	28	27	26	As per dataset	26	As per dataset	29	As per dataset[B]	27

[A] Default number of days as no data currently available
[B] Temperature data taken from April as no available temperature data for March

Figure 7. Percent of oxytocin remaining across the supply chain route with the longest transport durations - supply chain starting in January

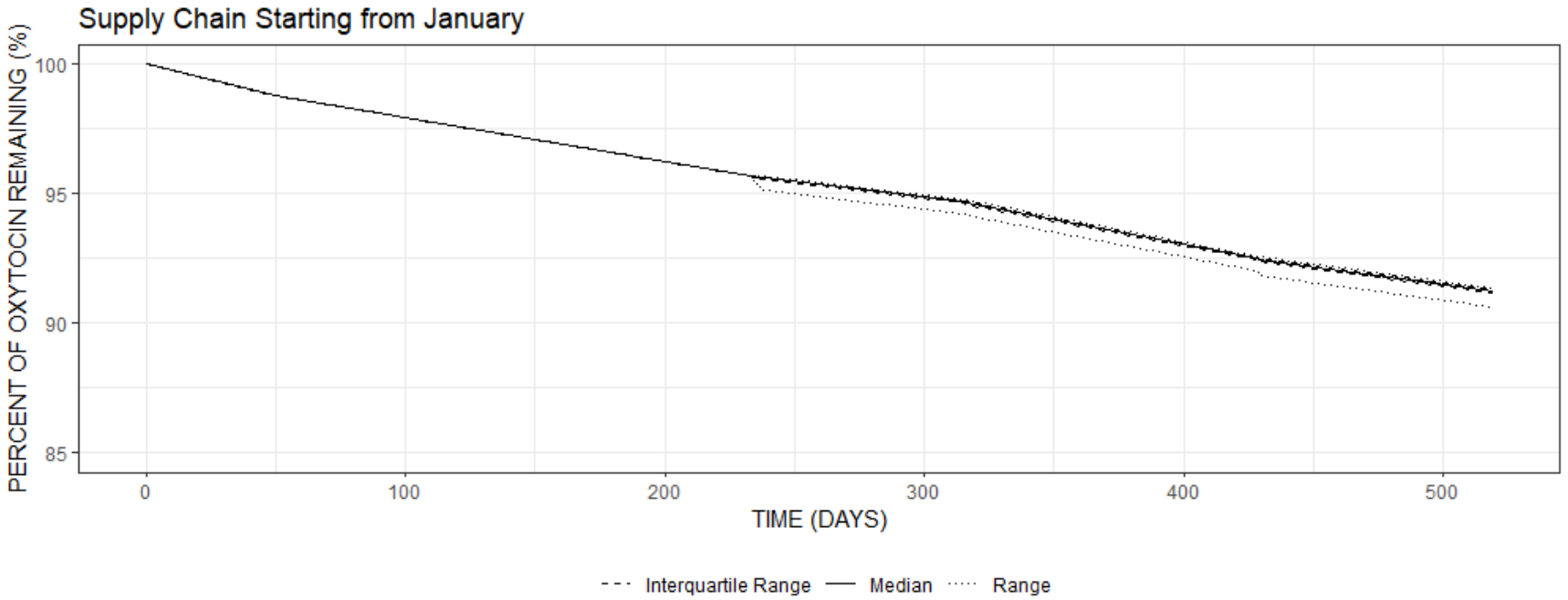
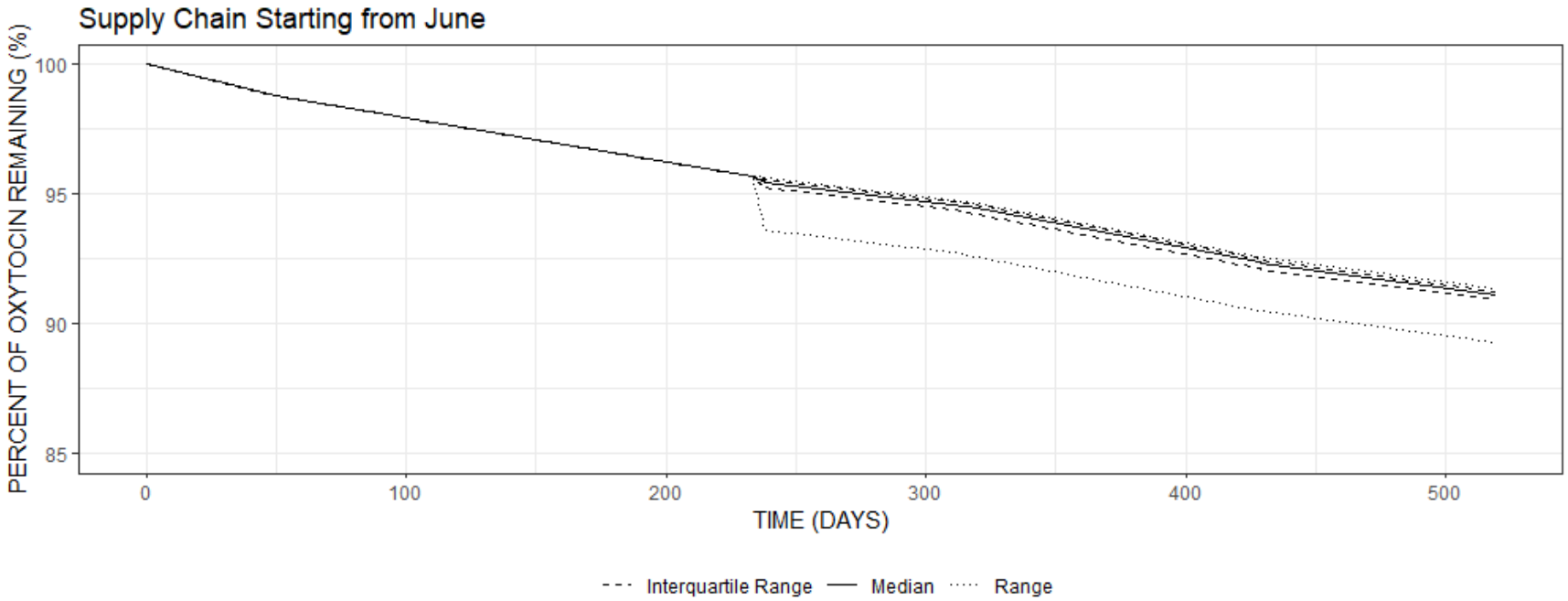


Table 4. Temperature and time spent at locations along supply chain route with longest transport durations – supply chain starting in June

		Ship	Port	Transport	Central	Transport	Provincial	Transport	District	Transport	Facility
Name		-	Maputo	-	Zimpeto	-	Niassa	-	de Marrupa	-	Marrupa
Days		50	3	0.02	180	5	77	1	112	1	90[A]
Month		Jun	Jul	Jul	Jul	Jan	Jan	Apr	Apr	Aug	Aug
Truck name		-	-	-	-	Foselev	-	Inhambane DPM	-	Tete Angonia	-
Temp (°C)	**Kit**	30	28	27	26	As per dataset	26	As per dataset	29	As per dataset	27

[A] Default number of days as no data currently available

Figure 8. Percent of oxytocin remaining across the supply chain route with the longest transport durations - supply chain starting in June



Implications and options for consideration

As illustrated in the findings, much of Mozambique's oxytocin is at a high risk of becoming substandard by the time it reaches the patient. Given high ambient temperatures in warehouses, facilities, and especially during in-country transportation, additional care and actions are likely needed to help ensure that oxytocin is of good quality when it is administered to the patient. Ensuring that only high quality, oxytocin labelled for storage between 2-8 degrees remains an important pillar of future strategies and actions to ensure oxytocin quality. Stakeholders may also want to consider other, or additional PPH products, in instances where end-to-end cold chain cannot be guaranteed. Additional detail on options for considerations are further described.

Ensure that only quality-assured, appropriately labelled oxytocin is registered, waivered, procured, and distributed.

Product labelling gives supply chain managers, pharmacists, and health care workers the information they need to store the product appropriately; if oxytocin is labelled for storage above 2-8 degrees C, it will most likely be stored under ambient, non-temperature controlled conditions. Ambient temperatures in Mozambique are too high for ambient storage of oxytocin and will contribute to more rapid product degradation, which is why oxytocin injection labelled for storage outside of the fridge is inappropriate. It is also worth echoing recommendations from the 2018 PQM report, which encourages the DNF to establish a standardized and rigorous process for registering or otherwise authorizing medicines[3]. In instances where rigorous testing is not an option, sourcing oxytocin that is appropriately labelled and has received approval from a stringent regulatory body or is WHO prequalified may be appropriate.

Consider removing oxytocin from essential medicines kits and where appropriate, replace it with oral misoprostol for PPH. Additionally, consider halting practice of returning unused oxytocin to district level for redistribution to high demand hospitals and facilities.

Including oxytocin in essential medicines kits is not appropriate in Mozambique due to its warm climate. The PQM report additionally documented oxytocin storage in temperatures outside of manufacturer specifications, and these results further support the finding that ambient storage of oxytocin will contribute to more rapid product degradation than is acceptable. Therefore, it is recommended that oxytocin is removed from essential medicines kits, and where appropriate, misoprostol be used to prevent and treat PPH. Additionally, when oxytocin arrives at facilities that do not manage it, it is often sent back to district warehouses for re-distribution. This practice is extremely high risk and should be discontinued.

Oral misoprostol is a safe and effective medicine to prevent and treat PPH and is a potential option for facilities that lack refrigerators and/or staff trained to administer injection products. Oral misoprostol does not require cold storage. Because essential medicines kits are currently part of the supply chain and typically directed towards low resource, rural facilities that often do not have electricity, oral misoprostol would solve practical and logistical challenges associated with oxytocin. This would also eliminate the issue of the additional time and associated degradation in cases where oxytocin is returned to the district level and then redistributed to other facilities. Heat stable carbetocin may also be considered; however, it is only indicated for PPH prevention and cannot be used to treat PPH. Therefore, it is not a substitute for oxytocin or misoprostol, so in cases where heat stable carbetocin is distributed, a treatment option must also be present.

Ensure that via classica oxytocin is stored in cold storage, irrespective of labelling. Effective communication on this point should be employed to help raise awareness and clarify any confusion.

Ideally, all oxytocin will be labelled for storage at 2-8 degrees C; however, the MOH may consider sending a notification to all facilities and warehouses indicating that oxytocin should be stored in cold storage as an interim measure in accordance with the WHO/UNFPA/UNICEF joint statement on appropriate storage and management of oxytocin[4]. Other countries – such as Ghana, Liberia, and Uganda – have employed this strategy and have observed some success. Following the issuance of a memo or notification, CMAM and partner staff should consider on-going monitoring to ensure compliance.

Reconsider shipment schedule and amount of time spent at each warehouse level.

Currently, oxytocin is ordered and delivered on an annual basis, and it spends approximately half a year in central level storage. By reducing the amount of time that each spends in the supply chain, it reduces the cumulative exposure to heat and subsequent product degradation. CMAM may want to consider changing the international shipment schedule to one that is quarterly instead of annual and changing stock min and max levels to accommodate this adjustment. This will effectively reduce the time spent in the supply chain by 50% and will substantially reduce the risk of time-temperature related degradation.

During international and domestic shipment and transportation, oxytocin should always be stored in cold storage, e.g., in refrigerated containers, refrigerated trucks, and/or in cold

boxes with ice. Transportation—including international ocean shipment and in-country transportation by truck—are the most significant risk points for oxytocin. Ocean shipment can take several months, and if oxytocin is not shipped in a refrigerated container, it will likely be exposed to higher that acceptable temperatures for a long duration. Interior truck temperatures can get extremely high, which results in rapid product degradation. During transport, oxytocin should always be kept under refrigeration or in cold boxes with ice.

Consider pairing uterotonic options with tranexamic acid to treat PPH.

While not specifically addressed in this analysis, it is worth considering the adoption and use of tranexamic acid for PPH treatment. In 2017, the results of the WOMAN Trial prompted WHO to update PPH treatment recommendations to unconditionally recommend the administration of tranexamic acid in conjunction with uterotonics to treat PPH[12]. Tranexamic acid is an antifibrinolytic that has historically been used in trauma setting to treat heavy bleeding. The results of the woman trail showed that tranexamic acid reduces death due to PPH related bleeding with no associated adverse effects (e.g. blood clots)[11]. Tranexamic acid does not require cold chain; however, it is administered intravenously and therefore requires a skilled health care provider for administration.

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Annex A. Detailed methodology

Compromised oxytocin quality may result from different causes: poor adherence to current Good Manufacturing Practices (cGMP) and excessive exposure to higher than acceptable temperatures. This activity examined procurement and supply chain management practices that may link to one or both causes. The activity was carried out in three phases, which aimed to:

1) Establish how oxytocin enters and moves through the supply chain from point of manufacture to the point of service delivery

2) Determine the duration and severity of temperature exposure throughout

3) Model oxytocin degradation to elicit major points of risk within the supply chain

Phase 1. Establish how oxytocin enters and moves through the supply chain

Documenting procurement practices and product flow

In the first phase, Mozambique's public sector procurement and sourcing practices were documented using a mix of key informant interviews and document review. GHSC-PSM analysts reviewed country policy and strategy documents, i.e., standard treatment guidelines, the national essential medicines list, and other strategy-related documents and held discussions with relevant in-country stakeholders. Regulatory practices were not examined in detail; however, a cursory review was carried out to inform and contextualize the analysis. Mozambique's list of registered oxytocin products and implementing partner reports, including quality testing results from the Promoting Quality Medicines Program, were consulted. Additional follow up with key informants was carried out as needed.

Phase 2. Determine the duration and severity of temperature exposure throughout

Estimating time spent in supply chain

To determine product flow and time spent in the supply chain, data from in-country logistics systems were extracted and analyzed. In Mozambique, data came from two systems: SIMAM and SIGLUS. The SIMAM system houses data on central-, provincial-, and district-level warehouses whereas SIGLUS contains data from service delivery points (i.e., hospitals and health facilities). Oxytocin issues or consumption data from at least the previous 12 months was required for all included facilities.

Issues data was used to approximate the frequency and amount of oxytocin moving through the supply chain at site level. Data was aggregated to the facility level to calculate the time periods between issues

to each site and the total amount issued. These metrics were used in combination with the data on the presence of fridges at each site, to select districts to include in the sample. For provinces with sufficient data, four districts were included in the sample based on whether a large proportion of facilities either had or did not have refrigerators, i.e., two districts with high refrigerator prevalence and two districts with low refrigerator prevalence. Notably, some provinces did not have any districts with enough refrigerators to meet inclusion criteria, in which case no district was selected for that category. The selected sites were then further examined by generating descriptive statistics for their frequency and amount of oxytocin issued.

To determine time spent in transit between the different levels of the supply chain, GHSC-PSM Mozambique field office staff were asked to estimate the transport time for routes between the central warehouse and provincial warehouses and provincial warehouses and the district warehouses, rounding to the nearest half day. To estimate the last mile (district warehouse to SDP) transportation times, GHSC-PSM Mozambique field office staff provided individual routing files in Microsoft Excel, from Project Last Mile, for individual provinces. Using the routes provided the estimated number of days spend in transport was extrapolated for each province (typically one day, or two days in some cases). This last-mile transport estimate was then applied to all routes for that province.

Estimating temperatures in warehouses and facilities

GPS location data was used to obtain modeled temperatures at each warehouse and health facility. This was done using the IBM Physical Analytics Integrated Data Repository and Services (IBM PAIRS) API, which includes modeled surfaces for external temperature. For a given range of time and GPS location, an API was used to return all available temperature data meeting those criteria. For this activity, data was obtained for the period of 1 Jan 2016 thru 1 Jan 2020. This data was obtained for all facility locations and was further processed. Resulting temperatures resulting were aggregated at the daily, weekly, and monthly levels for each facility and averaged across the four years. Temperature distributions were compared.

Estimating temperatures during in-country transportation

Temperature data during in-country transport was estimated using internal GHSC-PSM temperature and humidity monitoring IoT sensors from trucks that distribute medicines and supplies in Mozambique. These temperatures were aggregated up to the monthly and hourly level, taking the median value of all temperature reading occurring during a given hour and month.

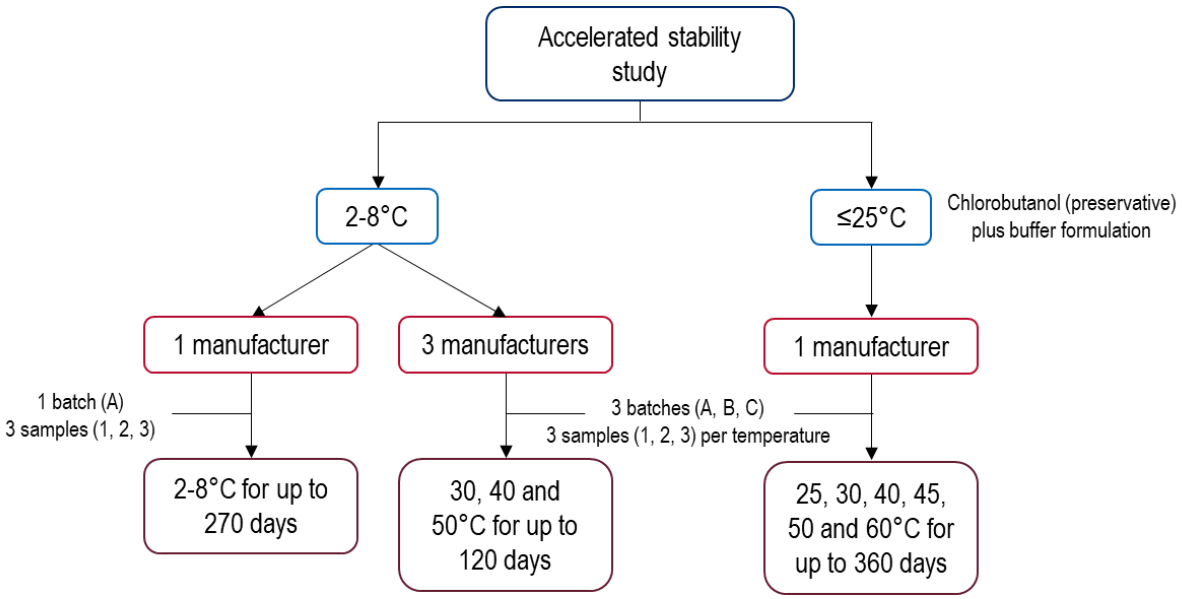
Phase 3. Model oxytocin degradation to elicit major points of risk within the supply chain

Data

Accelerated stability studies were conducted using oxytocin ampoules (10 IU/mL) obtained from four manufacturers (AS Grindeks, Biol, Biologici and RotexMedia). Three were labelled for storage between 2-8°C (AS Grindeks, Biologici and RotexMedia) and one was labelled for storage ≤25°C (Biol). The ampoules obtained from Biol contained a preservative (chlorobutanol) plus a buffer. This addition of a preservative and buffer is not expected to affect the degradation of oxytocin as compared ampoules labelled for storage at 2-8°C.

For ampoules labelled for storage between 2-8°C, the effect of constant storage at 30, 40 and 50°C was examined. The effect of constant storage at 2-8°C was also examined for oxytocin ampoules from AS Grindeks. For ampoules labelled for storage ≤25°C, the effect of constant storage at 25, 30, 40, 45, 50 and 60°C was examined. Details regarding the number of batches and samples obtained from each manufacturer, and the duration the ampoules were kept at the respective temperatures are detailed below.

Batch and sample details, by manufacturer



Schedule of analysis by temperature for samples evaluated during stability testing

	Storage Temperature						
Storage Duration	2-8°C	25°C	30°C	40°C	45°C	50°C	60°C
Day 0	✓	✓	✓	✓	✓	✓	✓
Day 5							✓
Day 10							✓
Day 15			✓	✓	✓	✓	✓
Day 30	✓	✓	✓	✓	✓	✓	✓
Day 60	✓	✓	✓	✓	✓	✓	✓
Day 90	✓	✓	✓	✓	✓	✓	
Day 120	✓	✓	✓	✓	✓	✓	
Day 180	✓	✓	✓				
Day 270	✓	✓	✓				
Day 360		✓	✓				

Estimating amount of oxytocin remaining in the vial

It has been previously reported that the degradation of oxytocin can be described by the Arrhenius equation below.

$$k = A\, e^{\frac{-EA}{RT}}$$

where *k* is the degradation rate constant, *A* is the pre-exponential factor, *EA* is the activation energy, *R* is the gas constant and *T* is temperature in Kelvin. *A* and *EA* were estimated using the naïve-pooled approach (i.e. no between-ampoule variability) with an additive residual error model using NONMEM (version 7.3) software. Using the estimates of *A* and *EA*, *k* was able to be calculated for each temperature investigated, which in turn was used to determine the amount of oxytocin remaining in the ampoule over time using the equation below.

$$A_{oxy} = A_{oxy,0} \cdot e^{-k \cdot t}$$

where A_{oxy} is amount of oxytocin in the ampoule at time t, $A_{oxy,0}$ is amount of oxytocin in the ampoule at time 0, which was set at 10 IU (equivalent to 16.7 mcg). The amount remaining in the vial over time at different temperatures was simulated in R (version 3.6.1).

Simulating supply routes in Mozambique

Oxytocin ampoules were distributed either via classica (refrigerated throughout the entire supply chain) or via kits (kept at ambient temperature). In Mozambique, 60-75% of ampoules are distributed via classica, and 25-40% ampoules via kits. Simulations were conducted to show the effect of temperature on the amount of oxytocin remaining in the vial across the supply chain.

Data related to the temperature and time spent at each location along the supply route within Mozambique was supplied by USAID. The supply chain locations are: ship (from manufacturer to port) > port > transport > central warehouse > transport > provincial warehouse > transport > district warehouse > transport > facility.

Several assumptions were made regarding the supply chain. It was assumed that shipments were from either Europe or India, with the average estimated duration being 50 days on a ship (data provided by USAID). Studies of sea shipments of essential medicines in tropical regions have detected within-pack temperatures as high as 42.4°C[14]. A conservative ambient temperature of 30°C was chosen for the simulations. It was also assumed that transport from one location to the next was done via a closed truck. Following internal discussions, the following steps were taken to estimate the temperature within the truck:

1. Obtain the average ambient temperature at the start and end location, then take the average.
2. If the average temperature is greater than 25, 27, 30 or 35°C for a duration of 1, 2, 3 or 4 days, respectively, use the average ambient temperature.
3. If the average temperature is less than those values, then use 25, 27, 30 or 35°C for the respective day.

All temperatures remained constant in the simulations, which do not reflect any seasonal changes or hourly changes.

The supply chains that were simulated included the following:

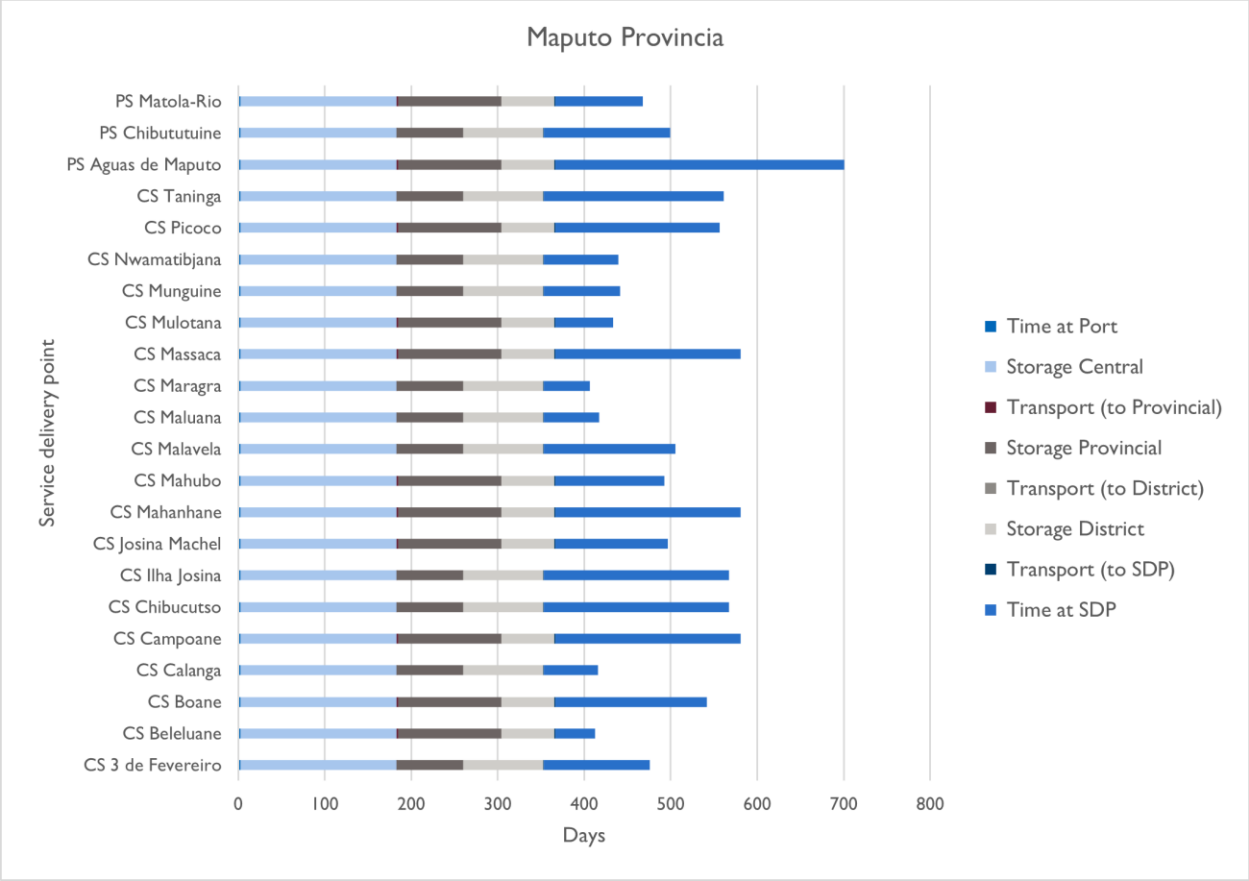
- Shortest route from the ship to the facility

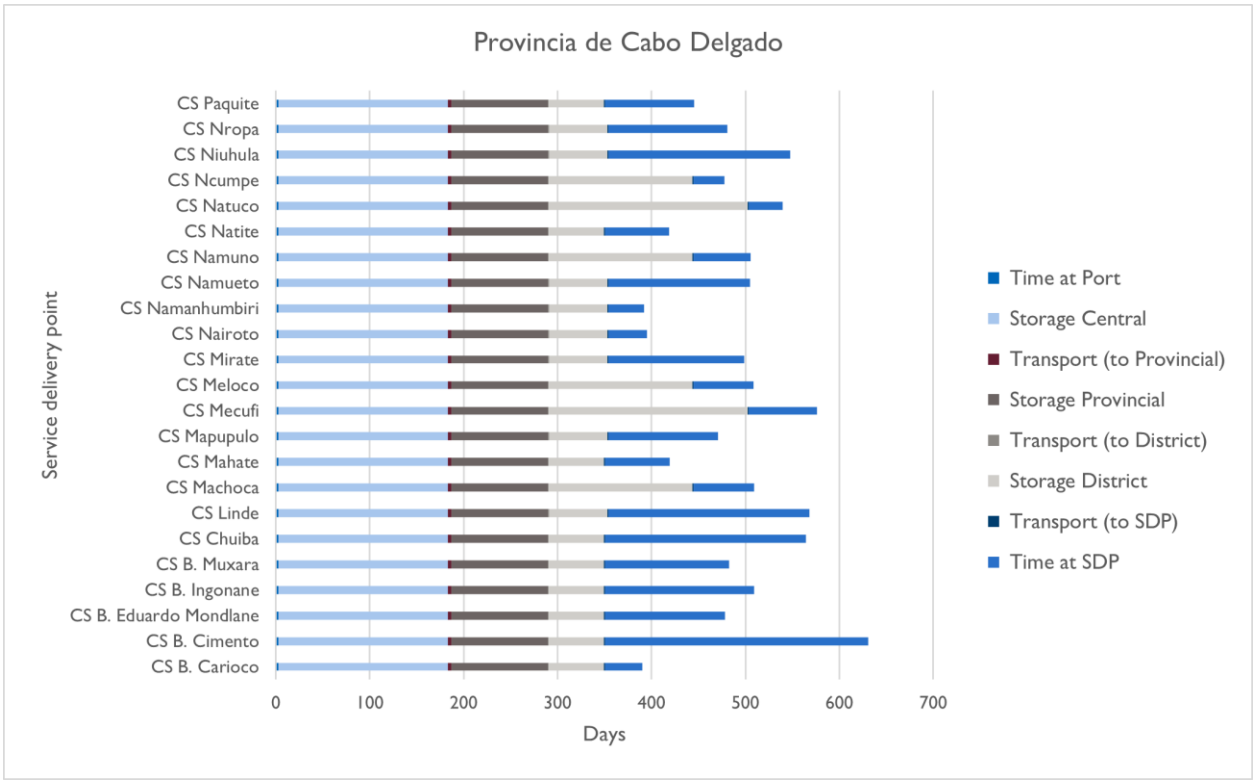
- Route with the longest time spent in transport
- Route with the highest ambient temperature

An interactive application was then developed in R (version 3.6.1) using the Shiny package (version 1.4.0). The application allows the temperature and duration at each location to be altered, which alters the corresponding graphs in real time. This interactive application is described in greater detail in Annex D.

The percent of oxytocin remaining during in-country transport was estimated using the model described above and the in-country transport temperature data (median, interquartile range and range). In the simulation dataset, the in-country transport temperature for Foselev was chosen for transport between central to provincial warehouses, Inhambane DPM for transport between provincial to district warehouses and Tete vehicle - Angonia from district warehouses to facilities. The in-country transport temperatures were then incorporated in the supply chain and the route with the longest time spent in transport was explored.

Annex B. Time spent in supply chain, facility level data organized by region




Provincia de Cabo Delgado
Service delivery point
CS Paquite
CS Nropa
CS Niuhula
CS Ncumpe
CS Natuco
CS Natite
CS Namuno
CS Namueto
CS Namanhumbiri
CS Nairoto
CS Mirate
CS Meloco
CS Mecufi
CS Mapupulo
CS Mahate
CS Machoca
CS Linde
CS Chuiba
CS B. Muxara
CS B. Ingonane
CS B. Eduardo Mondlane
CS B. Cimento
CS B. Carioco
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Transport (to Provincial)
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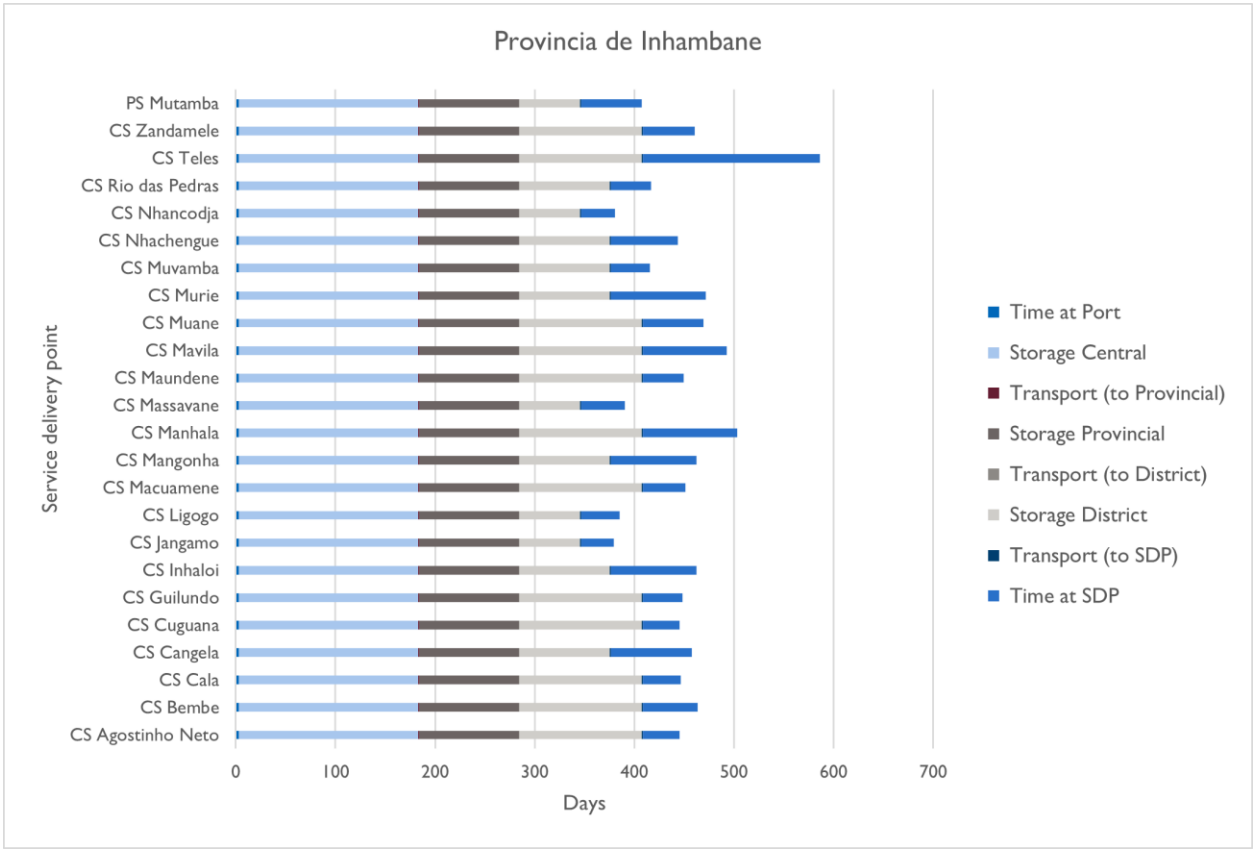
Storage District
Transport (to SDP)
Time at SDP


Provincia de Inhambane
Service delivery point
PS Mutamba
CS Zandamele
CS Teles
CS Rio das Pedras
CS Nhancodja
CS Nhachengue
CS Muvamba
CS Murie
CS Muane
CS Mavila
CS Maundene
CS Massavane
CS Manhala
CS Mangonha
CS Macuamene
CS Ligogo
CS Jangamo
CS Inhaloi
CS Guilundo
CS Cuguana
CS Cangela
CS Cala
CS Bembe
CS Agostinho Neto
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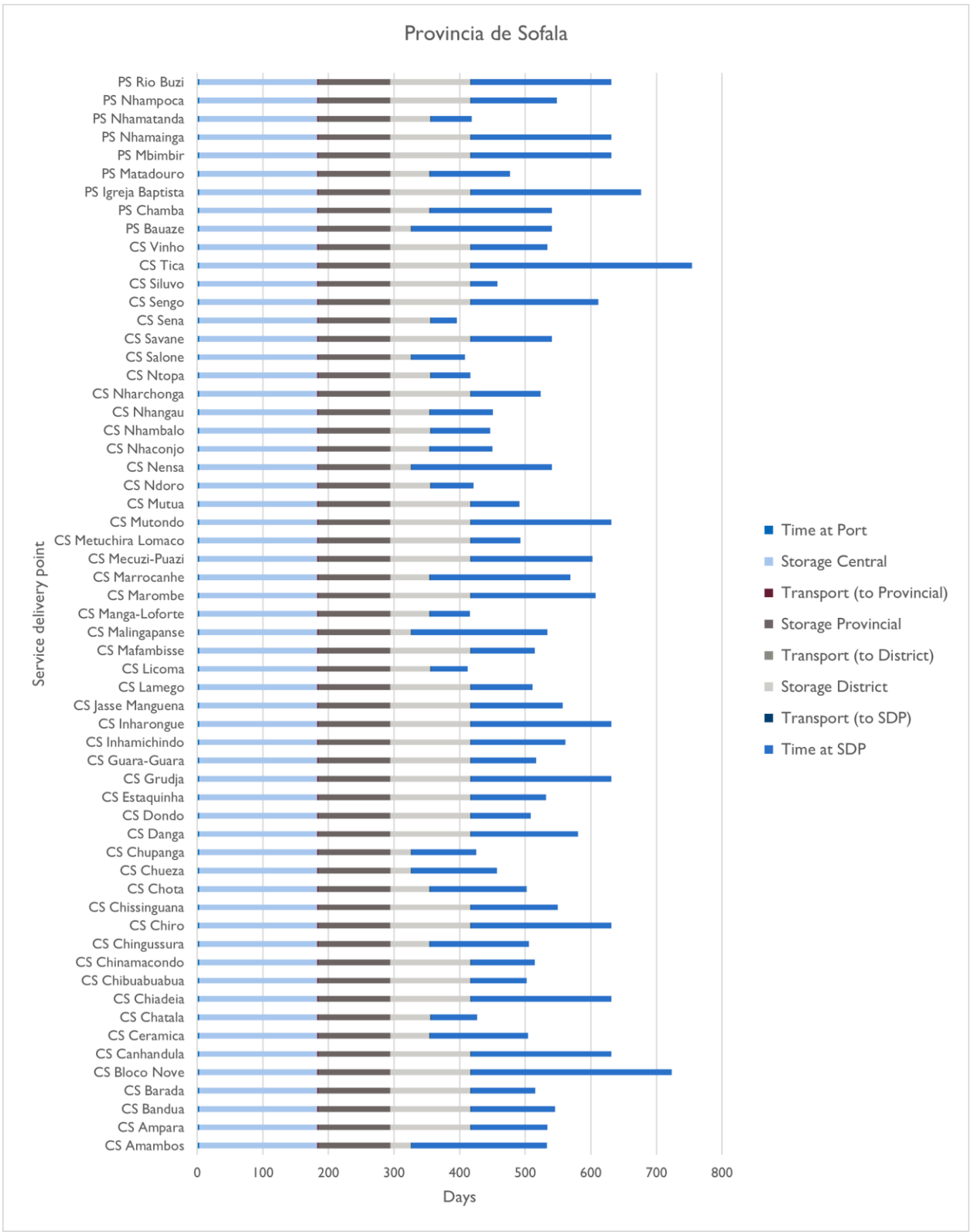
Provincia de Sofala
Service delivery point
PS Rio Buzi
PS Nhampoca
PS Nhamatanda
PS Nhamainga
PS Mbimbir
PS Matadouro
PS Igreja Baptista
PS Chamba
PS Bauaze
CS Vinho
CS Tica
CS Siluvo
CS Sengo
CS Sena
CS Savane
CS Salone
CS Ntopa
CS Nharchonga
CS Nhangau
CS Nhambalo
CS Nhaconjo
CS Nensa
CS Ndoro
CS Mutua
CS Mutondo
CS Metuchira Lomaco
CS Mecuzi-Puazi
CS Marrocanhe
CS Marombe
CS Manga-Loforte
CS Malingapanse
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CS Licoma
CS Lamego
CS Jasse Manguena
CS Inharongue
CS Inhamichindo
CS Guara-Guara
CS Grudja
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CS Dondo
CS Danga
CS Chupanga
CS Chueza
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CS Chiro
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CS Chinamacondo
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CS Canhandula
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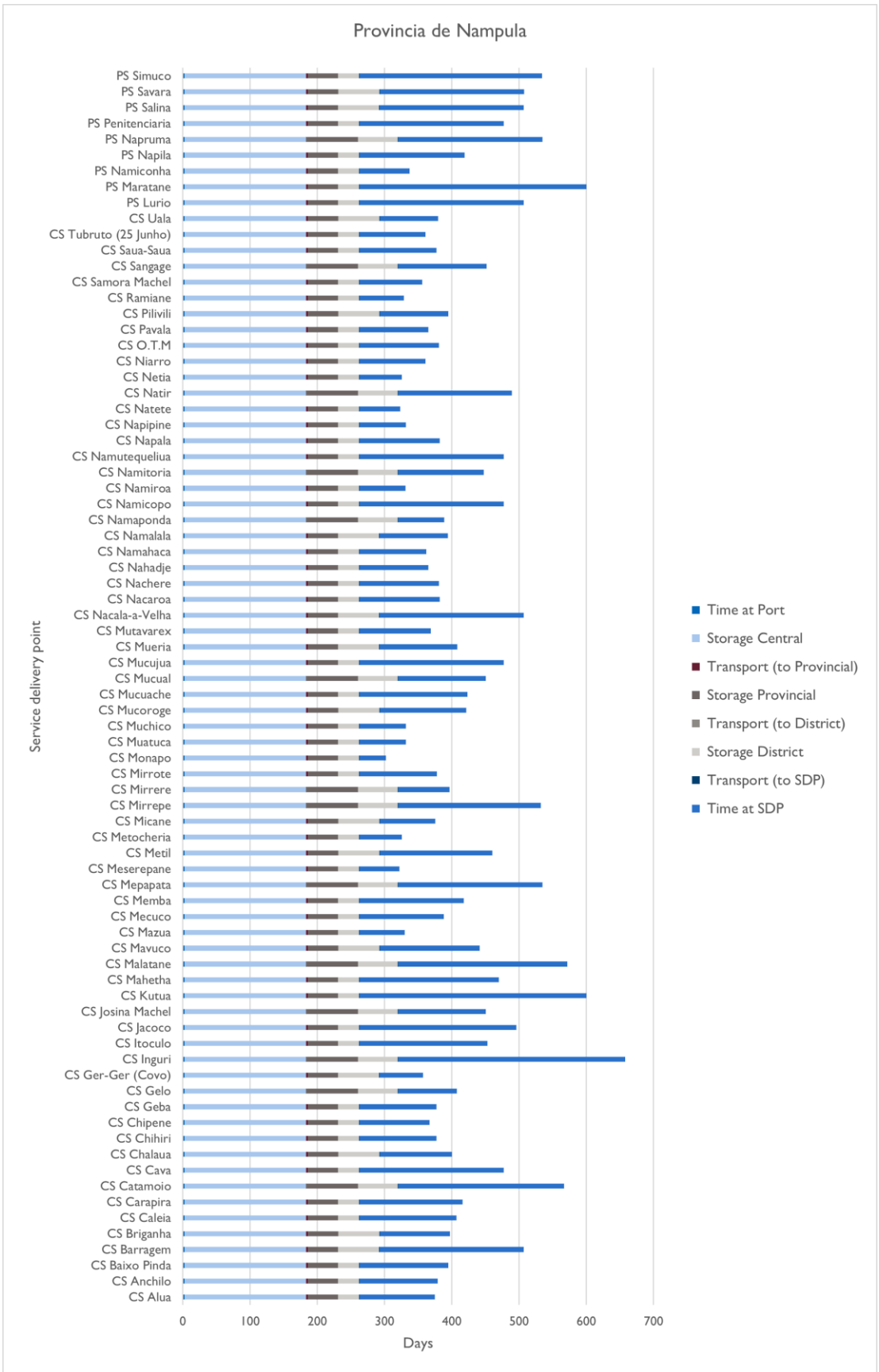
Provincia de Nampula
Service delivery point
PS Simuco
PS Savara
PS Salina
PS Penitenciaria
PS Napruma
PS Napila
PS Namiconha
PS Maratane
PS Lurio
CS Uala
CS Tubruto (25 Junho)
CS Saua-Saua
CS Sangage
CS Samora Machel
CS Ramiane
CS Pilivili
CS Pavala
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CS Metil
CS Meserepane
CS Mepapata
CS Memba
CS Mecuco
CS Mazua
CS Mavuco
CS Malatane
CS Mahetha
CS Kutua
CS Josina Machel
CS Jacoco
CS Itoculo
CS Inguri
CS Ger-Ger (Covo)
CS Gelo
CS Geba
CS Chipene
CS Chihiri
CS Chalaua
CS Cava
CS Catamoio
CS Carapira
CS Caleia
CS Briganha
CS Barragem
CS Baixo Pinda
CS Anchilo
CS Alua
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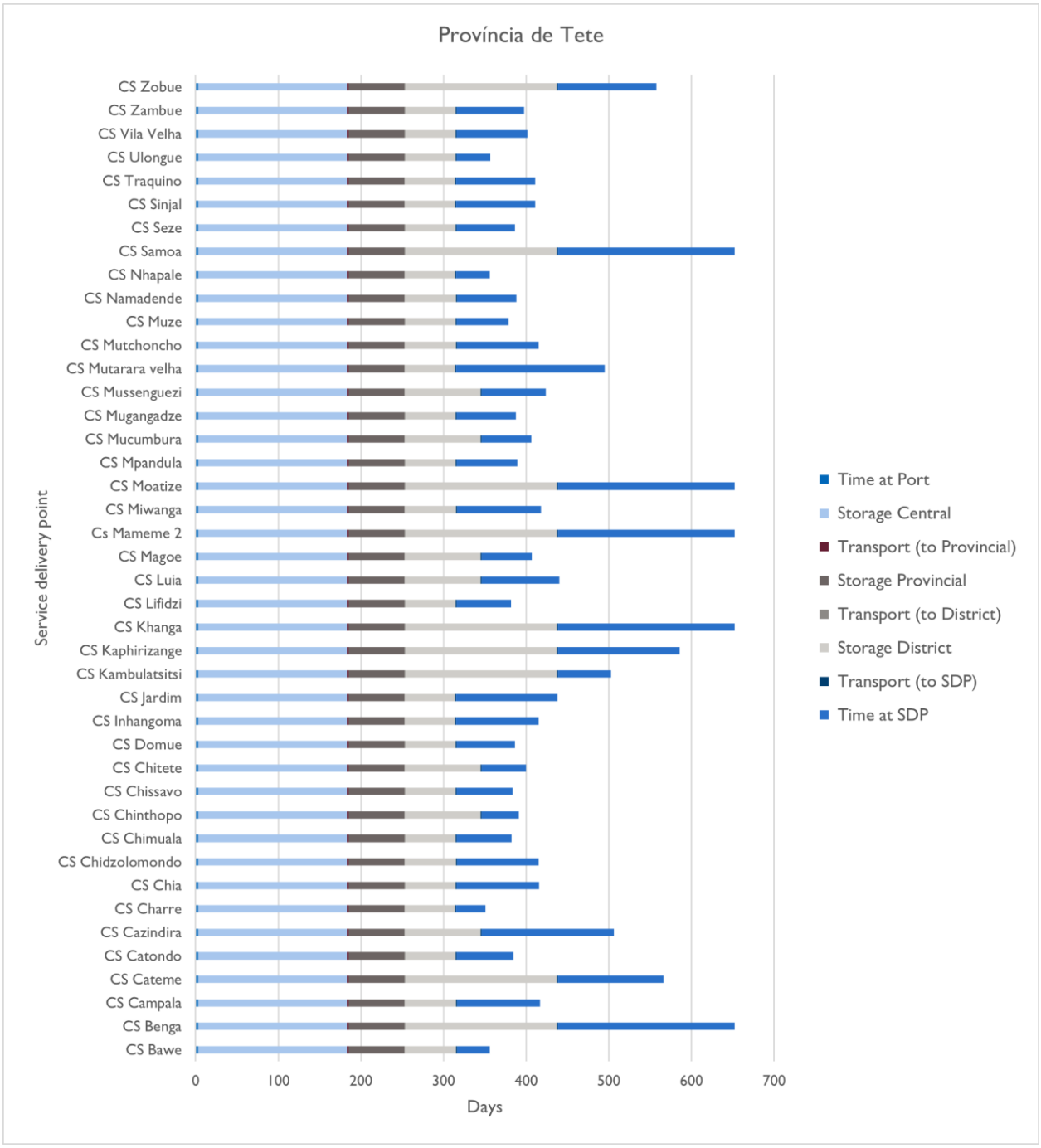
Província de Tete
Service delivery point
CS Zobue
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CS Ulongue
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CS Sinjal
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CS Nhapale
CS Namadende
CS Muze
CS Mutchoncho
CS Mutarara velha
CS Mussenguezi
CS Mugangadze
CS Mucumbura
CS Mpandula
CS Moatize
CS Miwanga
Cs Mameme 2
CS Magoe
CS Luia
CS Lifidzi
CS Khanga
CS Kaphirizange
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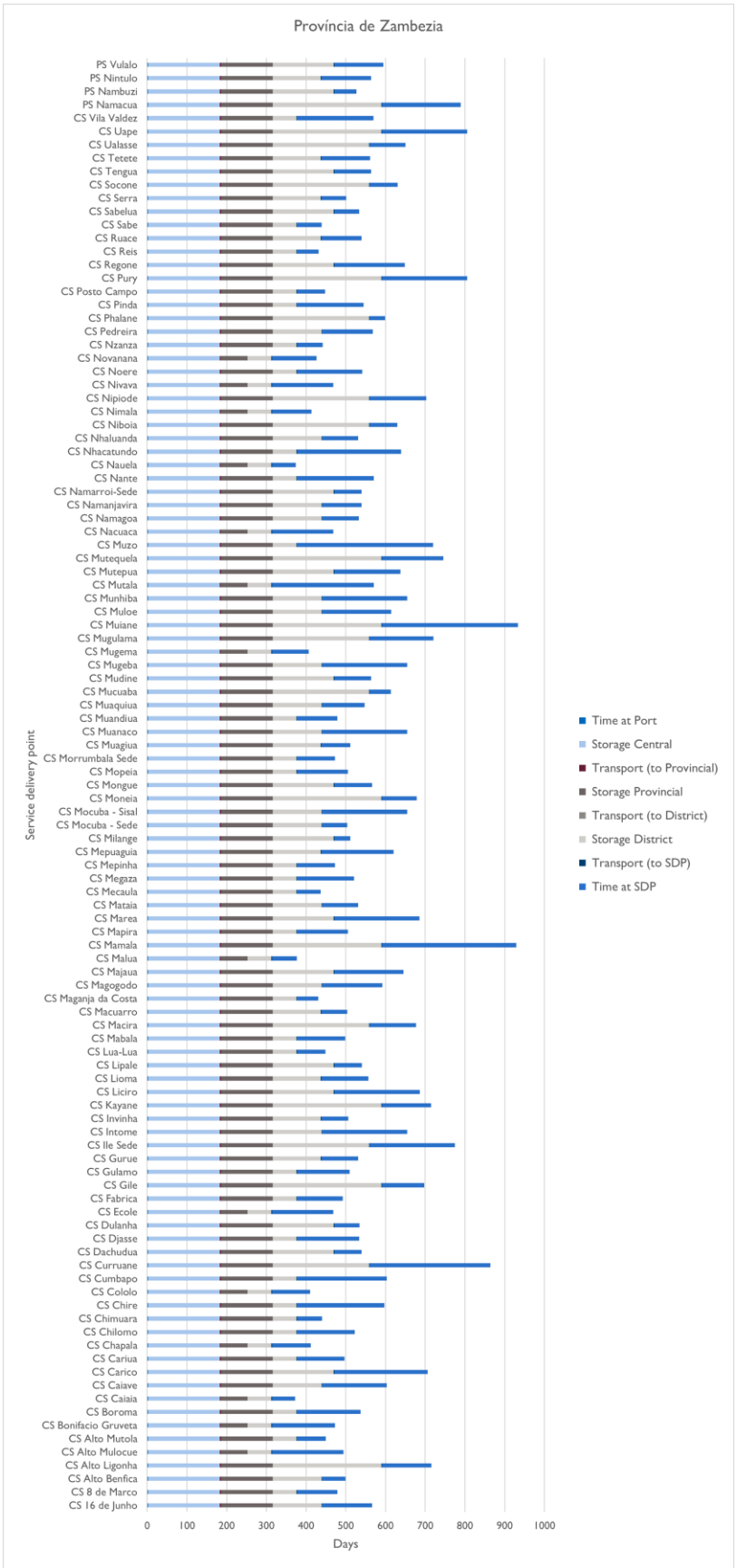
Time at SDP


Província de Zambezia
Service delivery point
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PS Nintulo
PS Nambuzi
PS Namacua
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CS Ualasse
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CS Tengua
CS Socone
CS Serra
CS Sabelua
CS Sabe
CS Ruace
CS Reis
CS Regone
CS Pury
CS Posto Campo
CS Pinda
CS Phalane
CS Pedreira
CS Nzanza
CS Novanana
CS Noere
CS Nivava
CS Nipiode
CS Nimala
CS Niboia
CS Nhaluanda
CS Nhacatundo
CS Nauela
CS Nante
CS Namarroi-Sede
CS Namanjavira
CS Namagoa
CS Nacuaca
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CS Mutequela
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CS Mocuba - Sede
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CS Mepuaguia
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CS Megaza
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CS Maganja da Costa
CS Macuarro
CS Macira
CS Mabala
CS Lua-Lua
CS Lipale
CS Lioma
CS Liciro
CS Kayane
CS Invinha
CS Intome
CS Ile Sede
CS Gurue
CS Gulamo
CS Gile
CS Fabrica
CS Ecole
CS Dulanha
CS Djasse
CS Dachudua
CS Curruane
CS Cumbapo
CS Cololo
CS Chire
CS Chimuara
CS Chilomo
CS Chapala
CS Cariua
CS Carico
CS Caiave
CS Caiaia
CS Boroma
CS Bonifacio Gruveta
CS Alto Mutola
CS Alto Mulocue
CS Alto Ligonha
CS Alto Benfica
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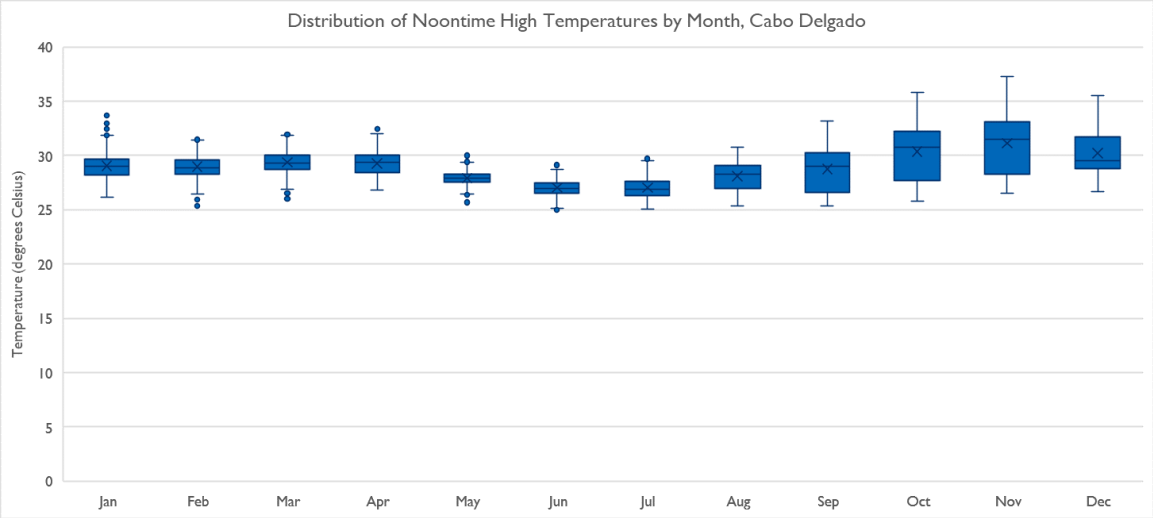
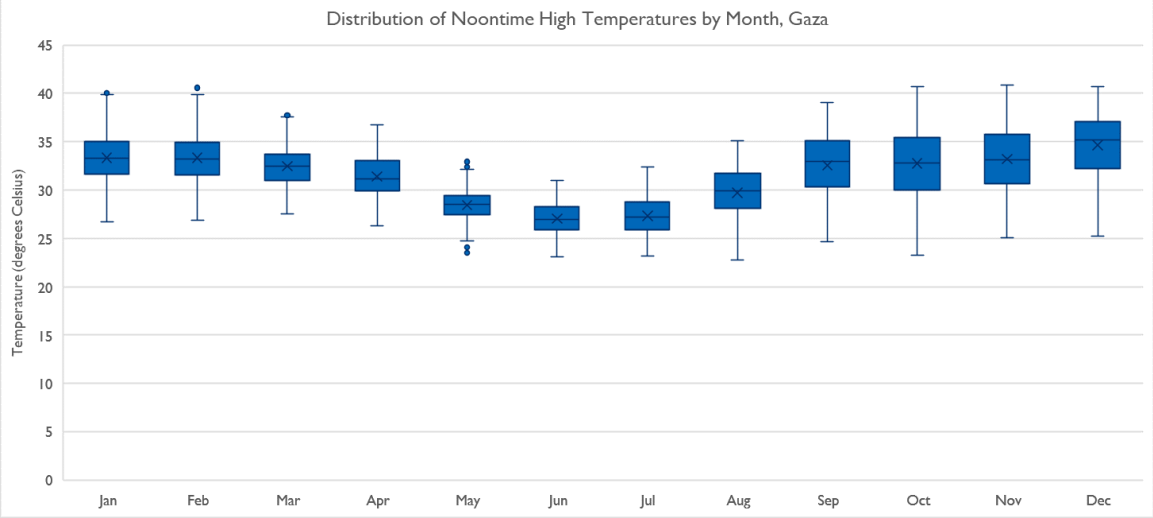
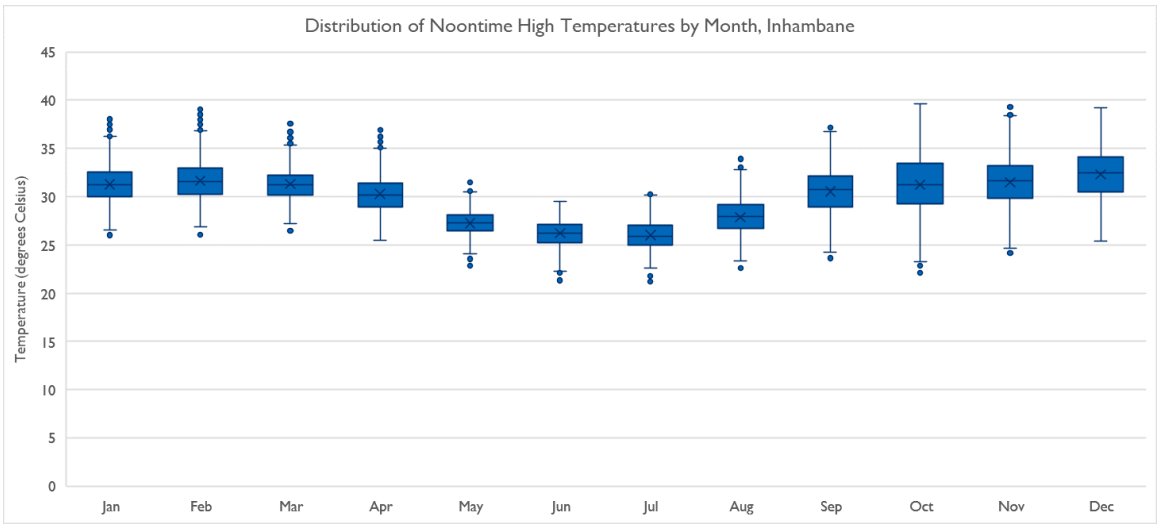
Transport (to SDP)
Time at SDP

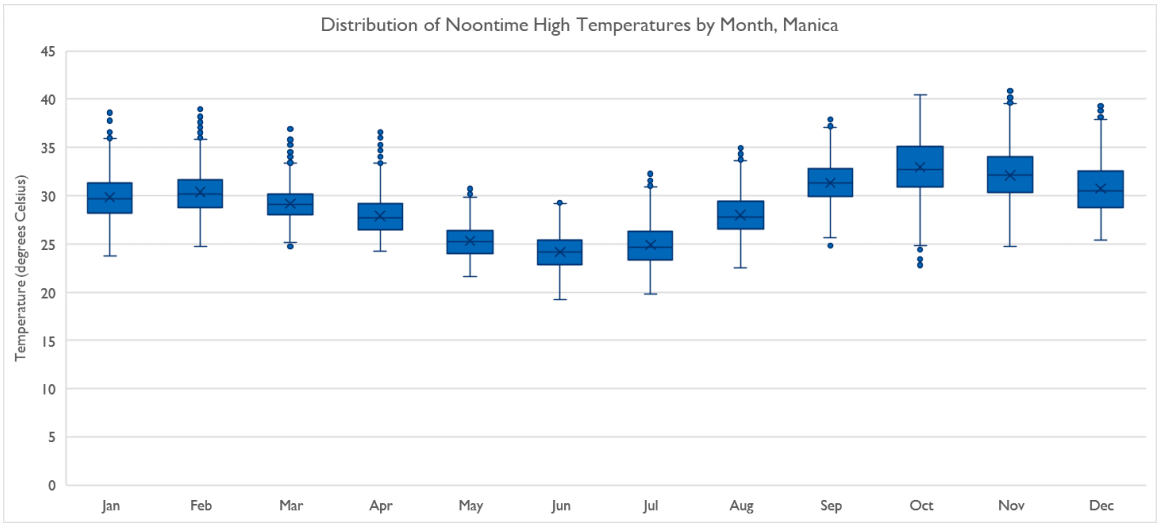
Annex C. Distribution of noontime temperatures at all included sites, disaggregated by region

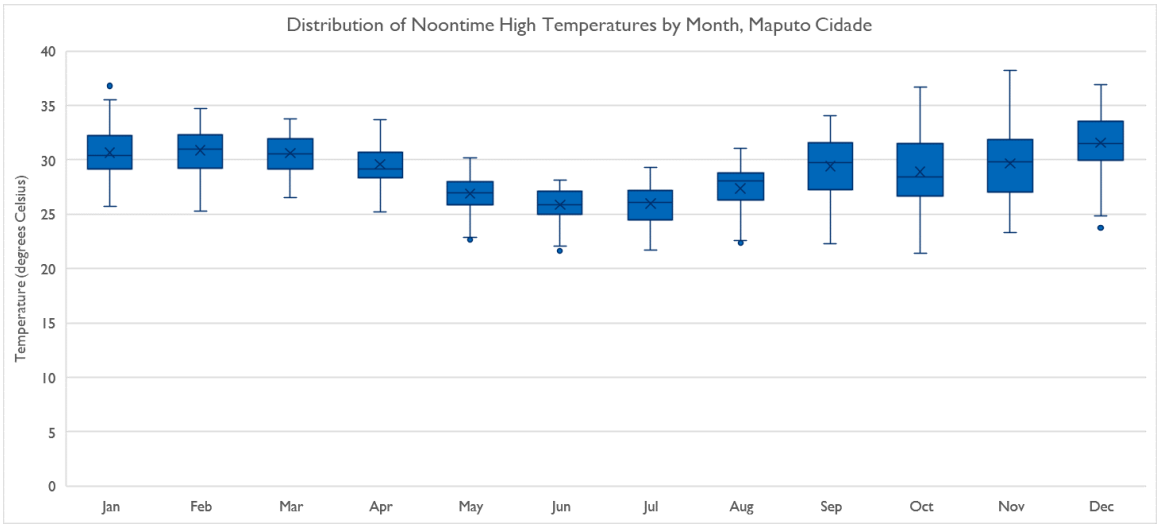
The distributions of noontime temperatures are further broken down by region. These data cover years 2016-2020.

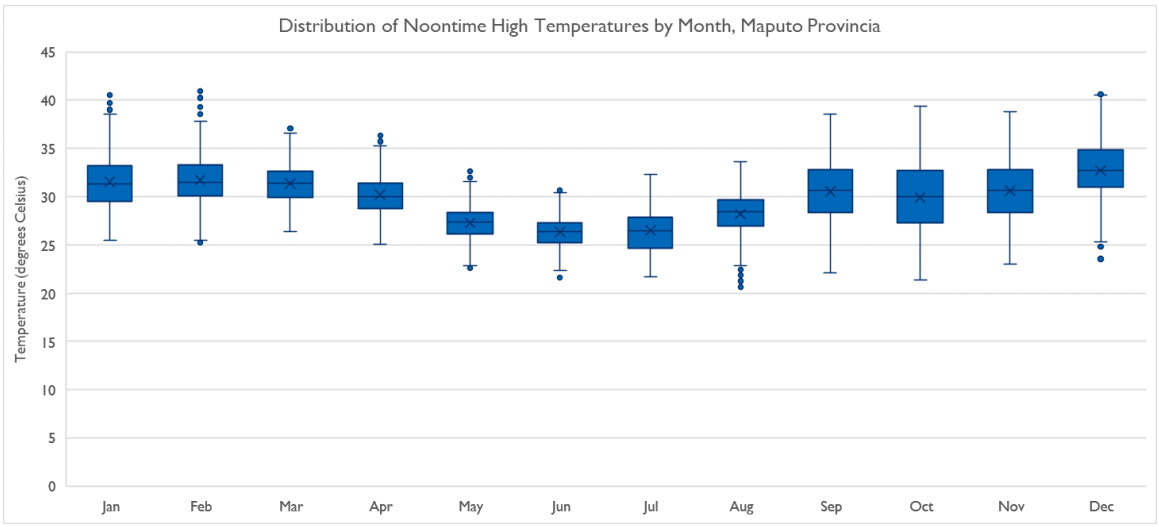


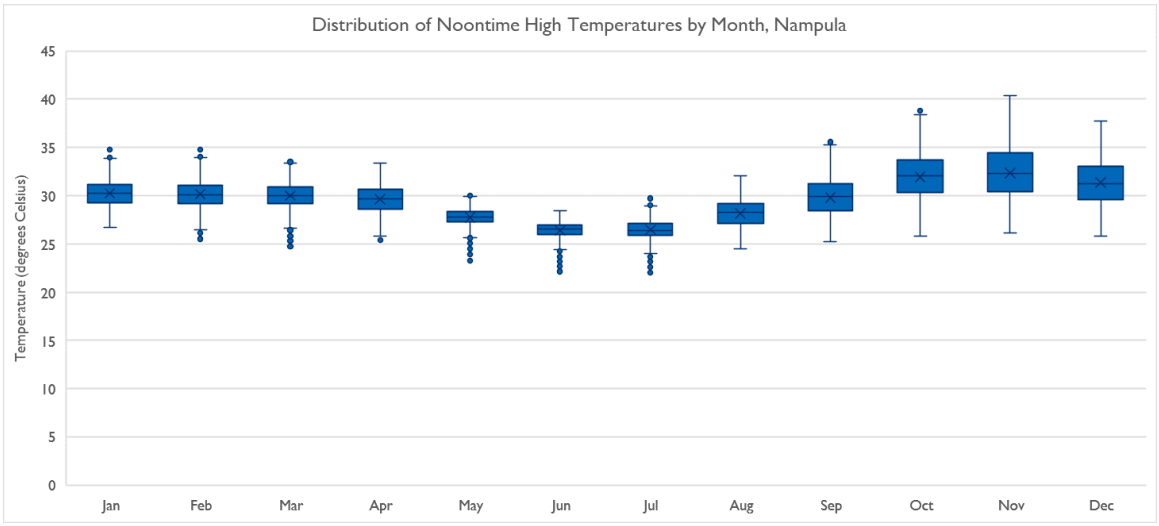


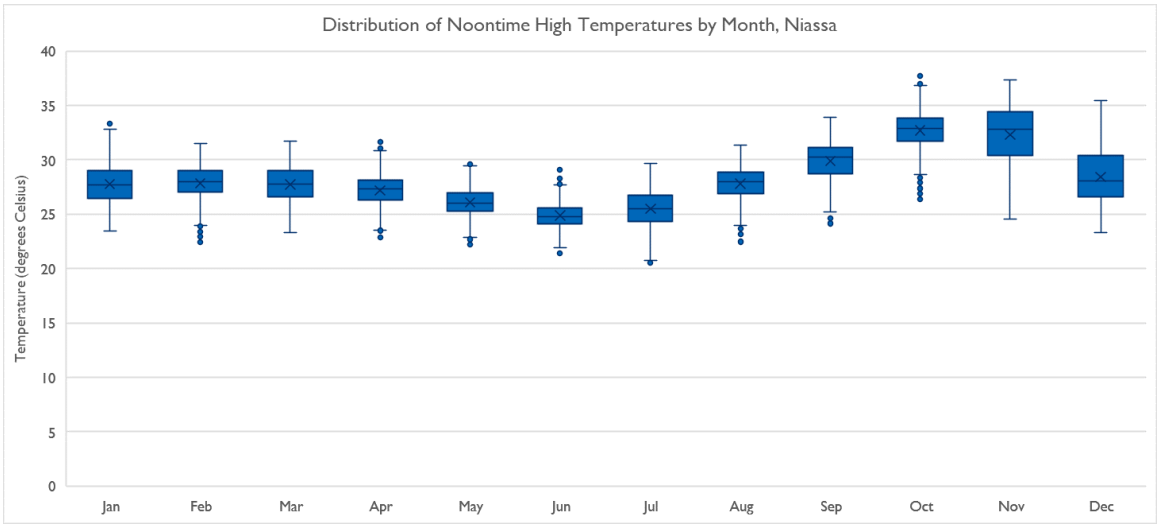

Distribution of Noontime High Temperatures by Month, Inhambane
Temperature (degrees Celsius)
45
40
35
30
25
20
15
10
5
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec

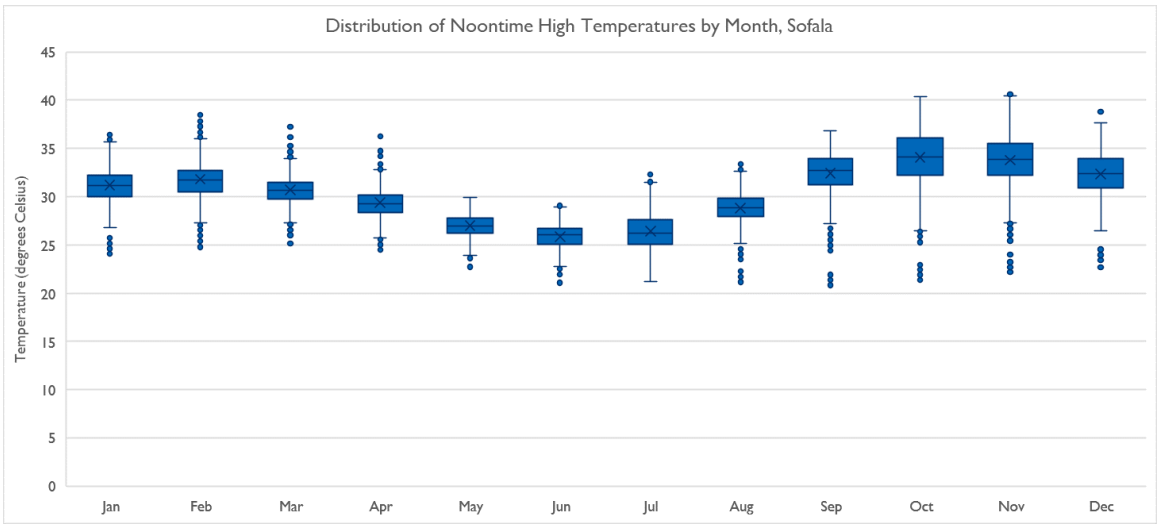

Distribution of Noontime High Temperatures by Month, Manica
Temperature (degrees Celsius)
45
40
35
30
25
20
15
10
5
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec

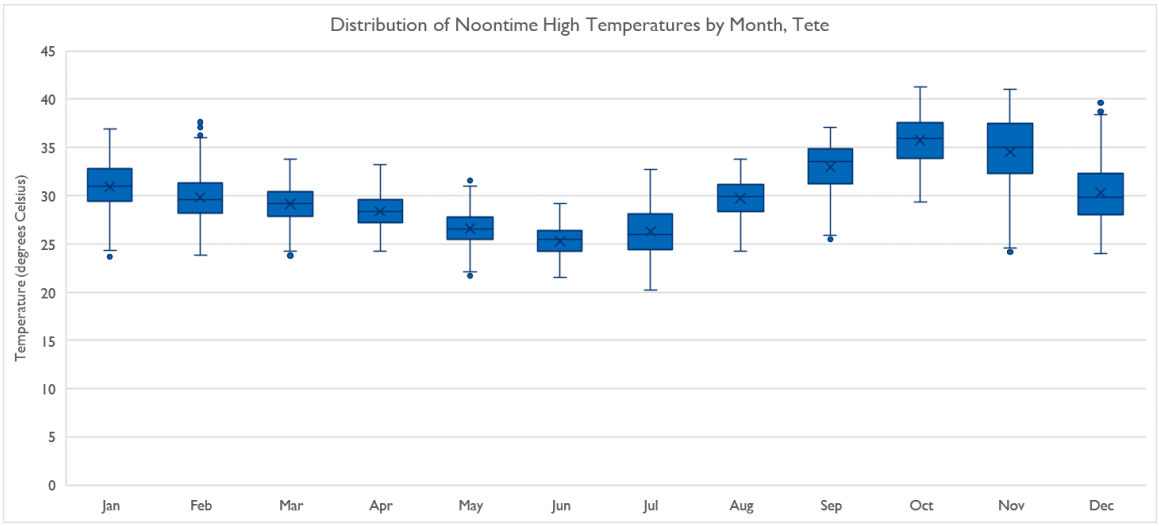

Distribution of Noontime High Temperatures by Month, Maputo Cidade
Temperature (degrees Celsius)
40
35
30
25
20
15
10
5
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec

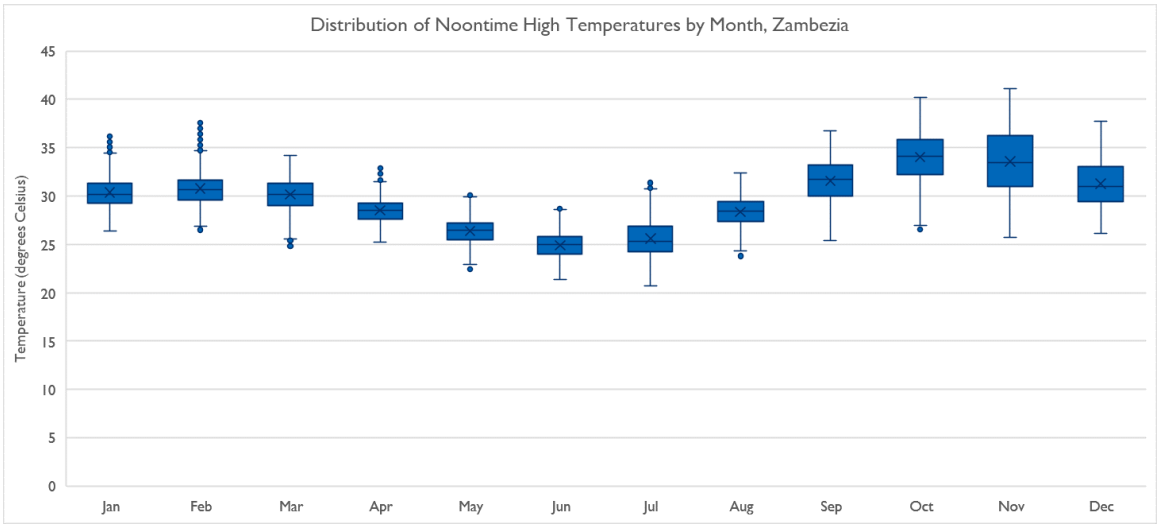

Distribution of Noontime High Temperatures by Month, Maputo Provincia
Temperature (degrees Celsius)
45
40
35
30
25
20
15
10
5
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec


Distribution of Noontime High Temperatures by Month, Nampula
Temperature (degrees Celsius)
45
40
35
30
25
20
15
10
5
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec


Distribution of Noontime High Temperatures by Month, Niassa
Temperature (degrees Celsius)
40
35
30
25
20
15
10
5
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec


Distribution of Noontime High Temperatures by Month, Sofala
Temperature (degrees Celsius)
45
40
35
30
25
20
15
10
5
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec


Distribution of Noontime High Temperatures by Month, Tete
Temperature (degrees Celsius)
45
40
35
30
25
20
15
10
5
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec

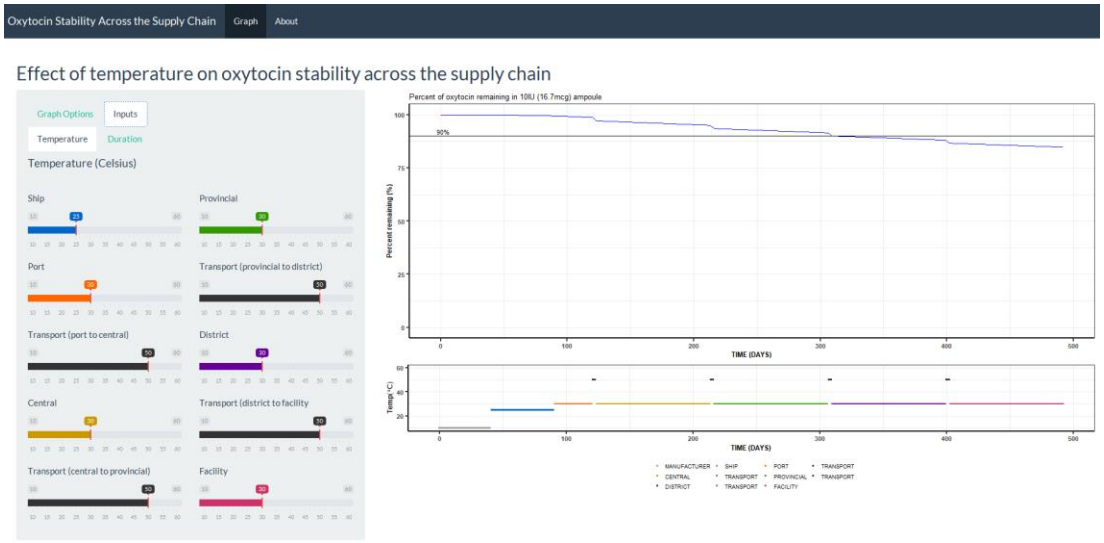

Distribution of Noontime High Temperatures by Month, Zambezia
Temperature (degrees Celsius)
45
40
35
30
25
20
15
10
5
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec

Annex D. Figures of the interactive application

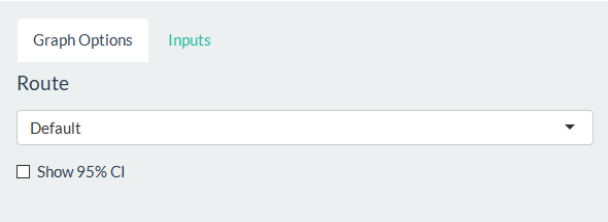
The figures below show a screenshot of the user interface which includes the following components:

- Side bar (left-hand side): temperature and duration tabs which allow temperature and duration spent at a location to be changed (e.g. temperature slider, duration numerical input).
- Main page (right-hand side): top graph shows the percent of oxytocin remaining in a 10IU ampoule across the supply chain, and bottom graph shows the temperature vs. time in days graph.

Please note that the settings shown in the two figures are default settings and do not reflect a pre-specified supply chain route.

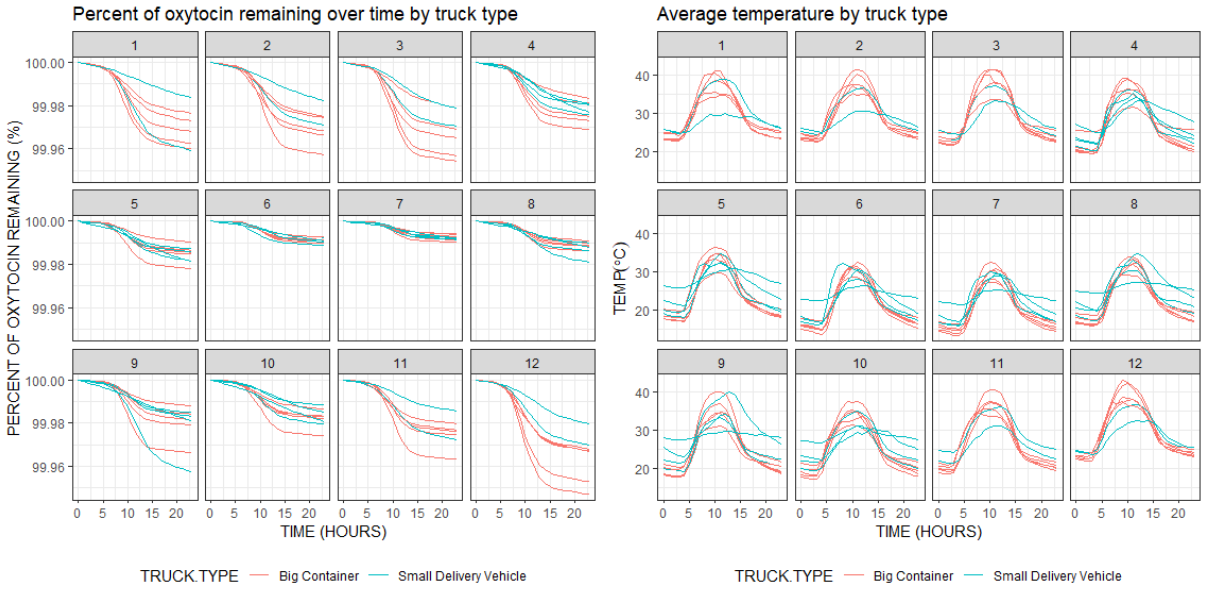


Other user interface options in the app include an option to select pre-specified routes (described in Annex.A, Phase 3) from a drop down box.

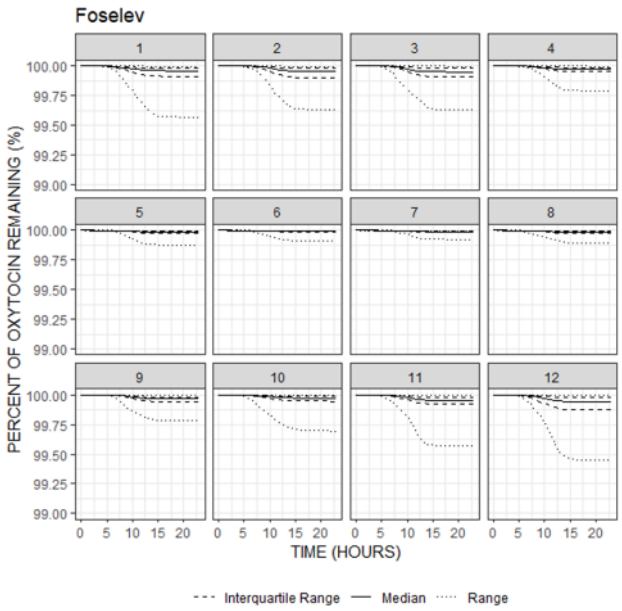


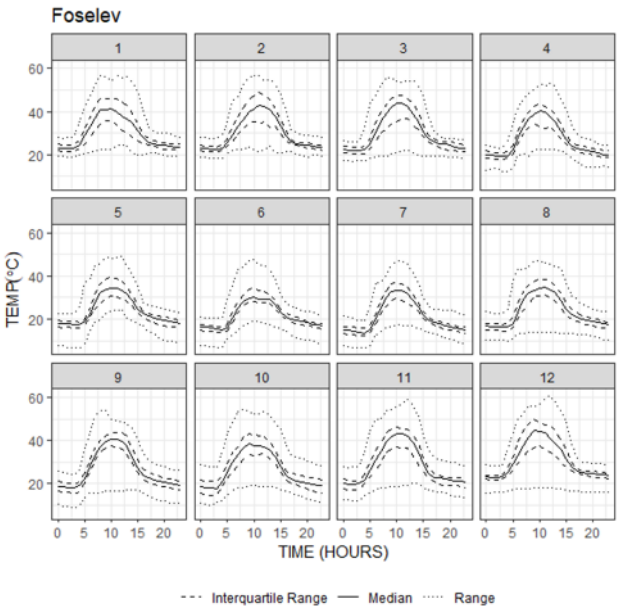
Annex E. Estimated percent of oxytocin remaining, stratified by truck type and truck name

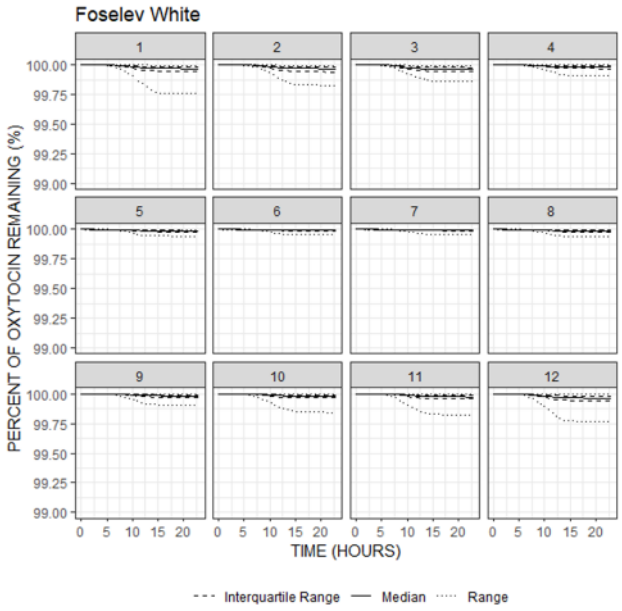
Stratification by truck type and month (1=January to 12=December)

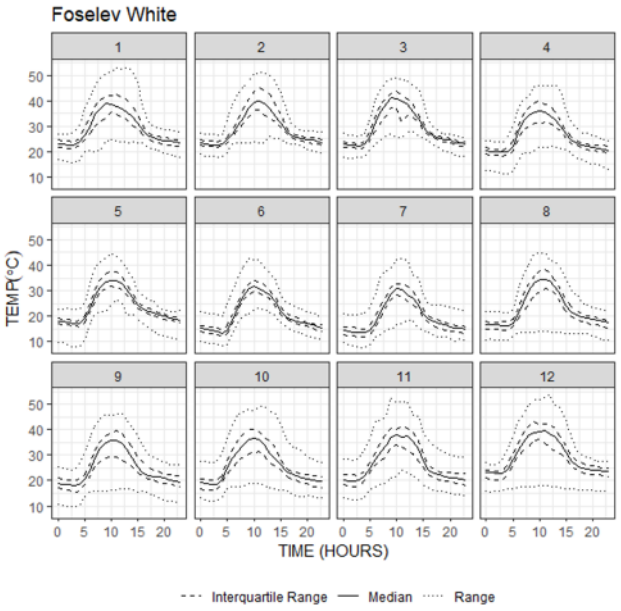


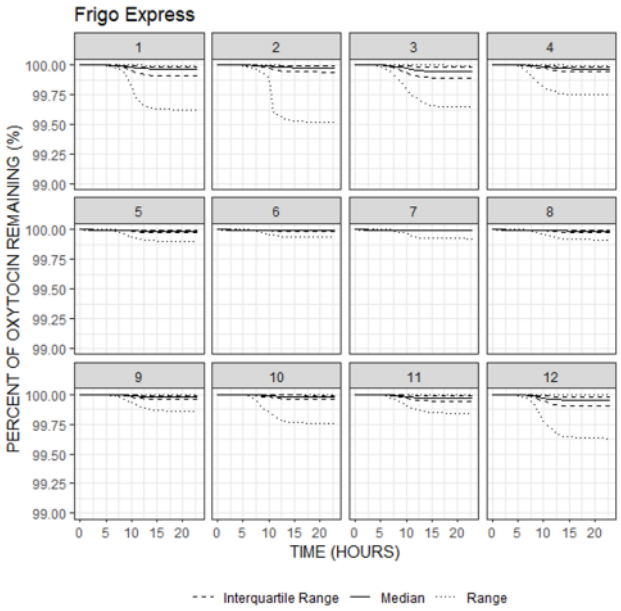
Stratified by truck and month (1=January to 12=December)

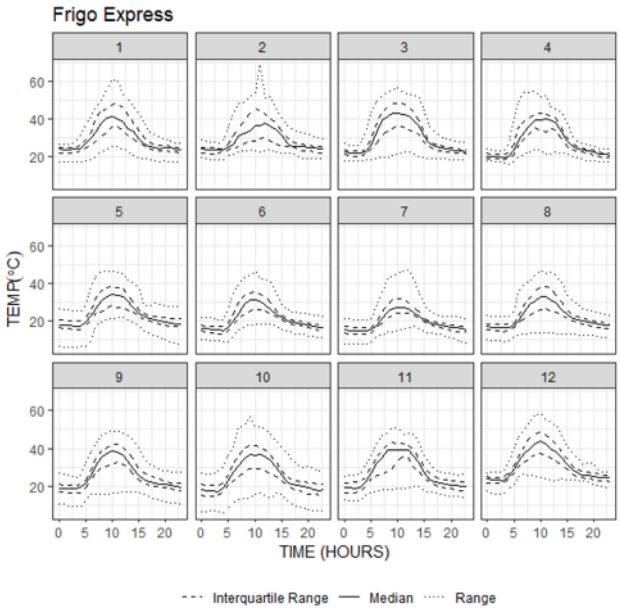


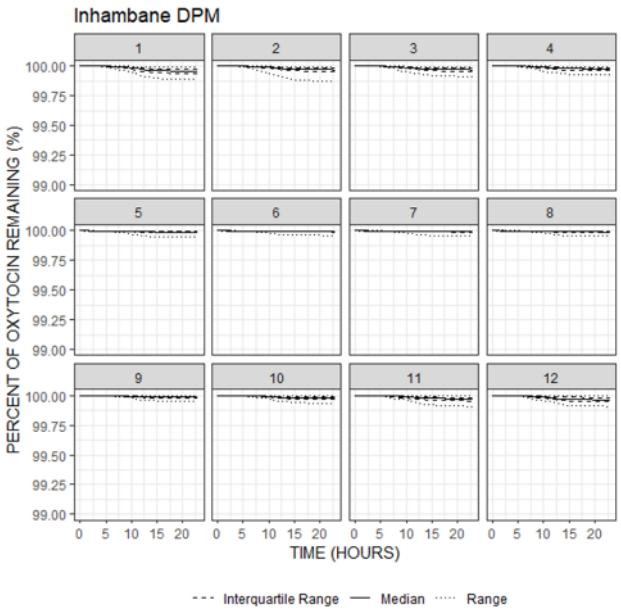


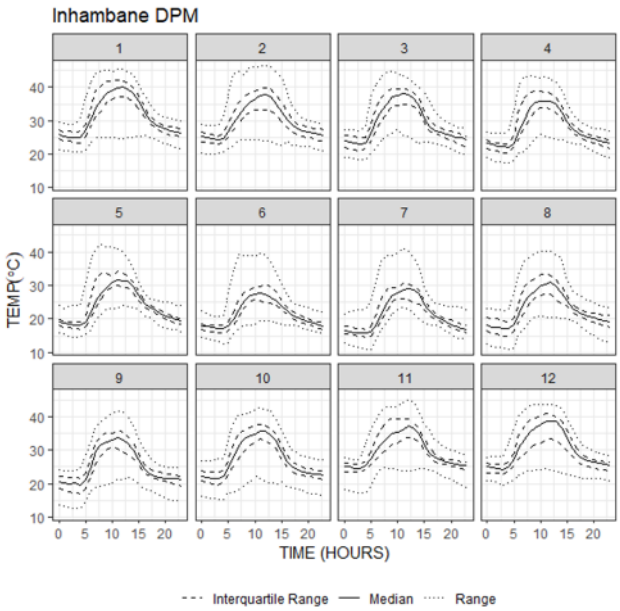


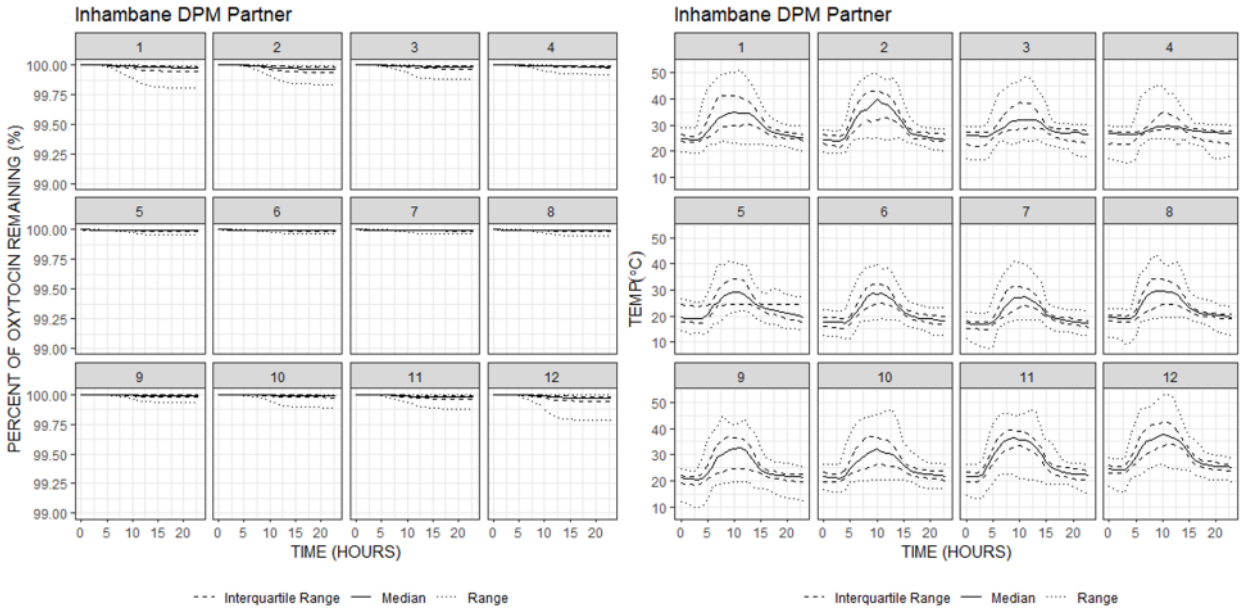


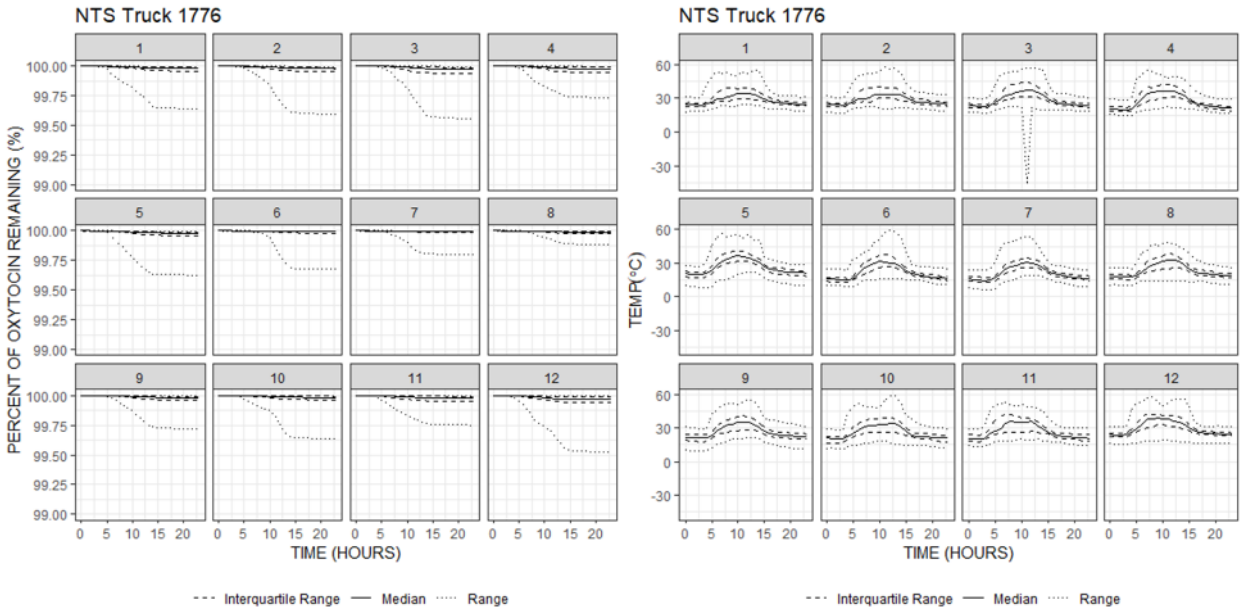

Frigo Express
PERCENT OF OXYTOCIN REMAINING (%)
TIME (HOURS)
Interquartile Range
Median
Range

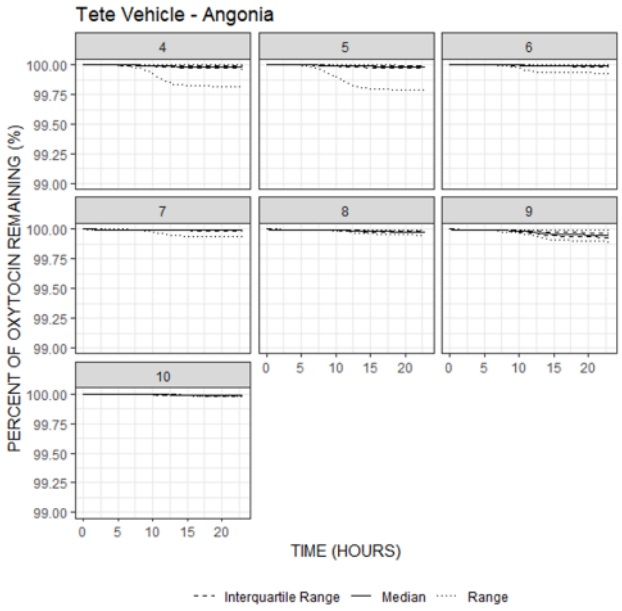

Frigo Express
TEMP(°C)
TIME (HOURS)
Interquartile Range
Median
Range

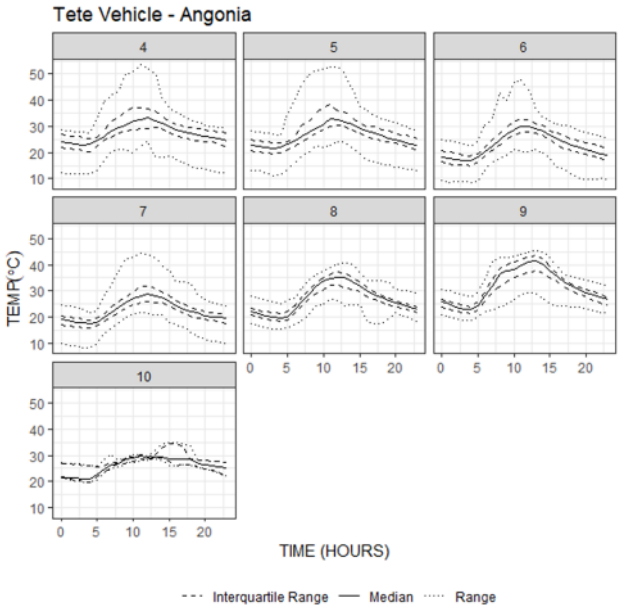

Inhambane DPM
PERCENT OF OXYTOCIN REMAINING (%)
TIME (HOURS)
Interquartile Range
Median
Range

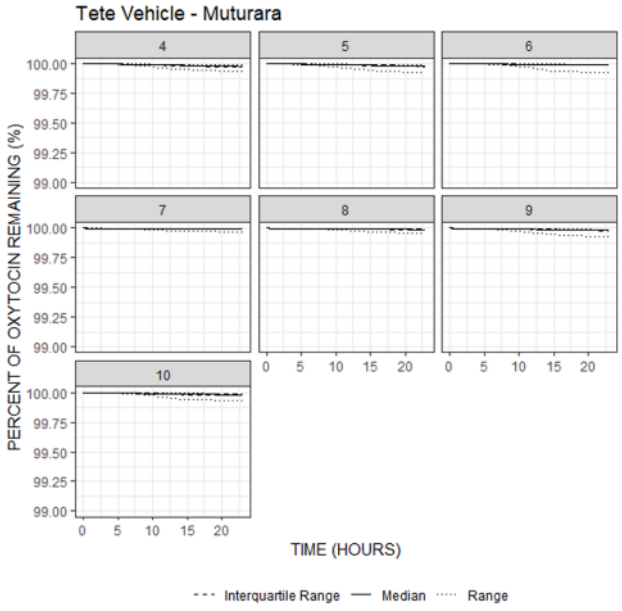

Inhambane DPM
TEMP(°C)
TIME (HOURS)
Interquartile Range
Median
Range

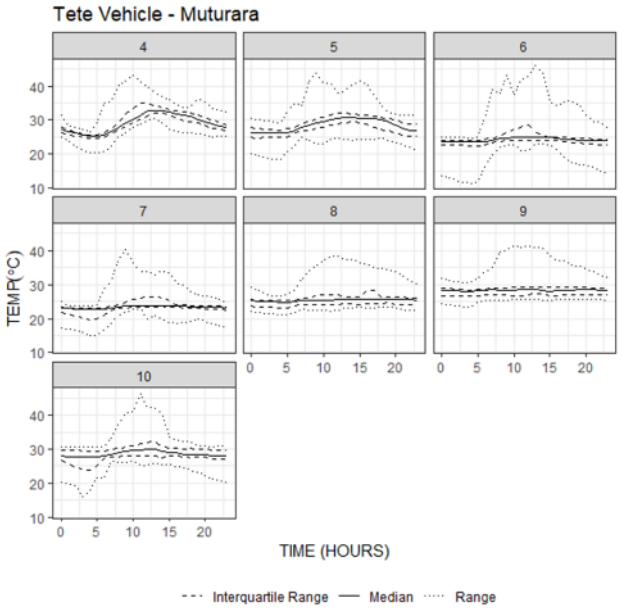

Inhambane DPM Partner
PERCENT OF OXYTOCIN REMAINING (%)
TIME (HOURS)
Interquartile Range
Median
Range
Inhambane DPM Partner
TEMP(°C)
TIME (HOURS)
Interquartile Range
Median
Range

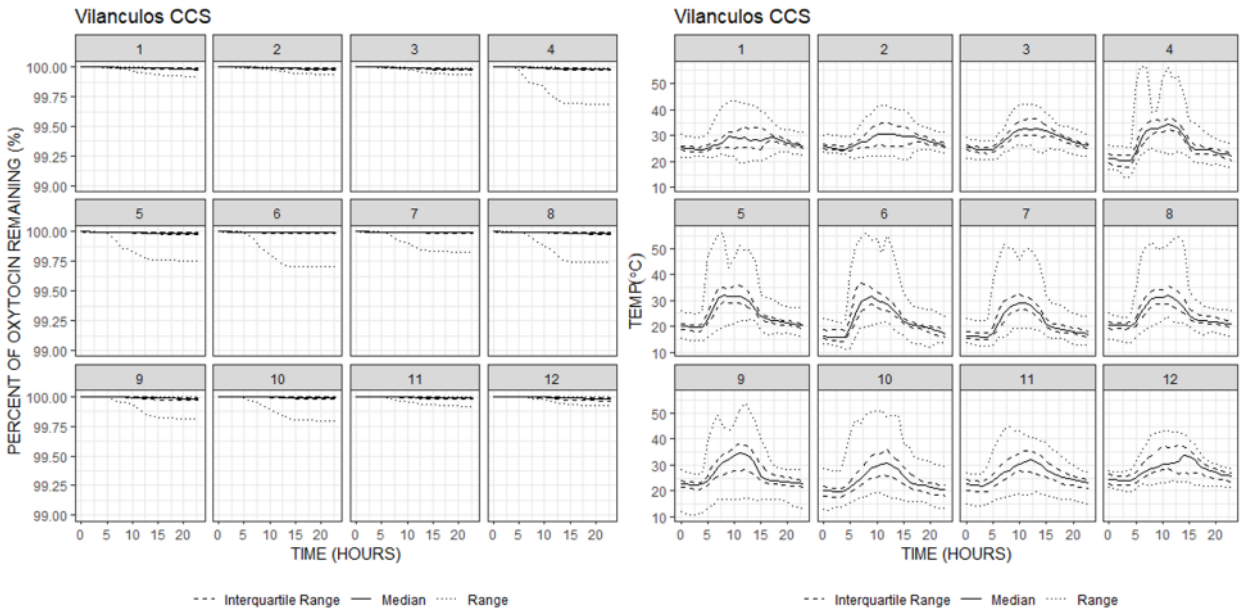

NTS Truck 1776
PERCENT OF OXYTOCIN REMAINING (%)
TIME (HOURS)
Interquartile Range
Median
Range
NTS Truck 1776
TEMP(°C)
TIME (HOURS)
Interquartile Range
Median
Range


Tete Vehicle - Angonia
PERCENT OF OXYTOCIN REMAINING (%)
TIME (HOURS)
Interquartile Range
Median
Range


Tete Vehicle - Angonia
TEMP(°C)
TIME (HOURS)
Interquartile Range
Median
Range


Tete Vehicle - Muturara
PERCENT OF OXYTOCIN REMAINING (%)
TIME (HOURS)
Interquartile Range
Median
Range


Tete Vehicle - Muturara
TEMP(°C)
TIME (HOURS)
Interquartile Range
Median
Range


Vilanculos CCS
PERCENT OF OXYTOCIN REMAINING (%)
TIME (HOURS)
Interquartile Range
Median
Range
Vilanculos CCS
TEMP(°C)
TIME (HOURS)
Interquartile Range
Median
Range

Annex F. List of Registered Oxytocin and Misoprostol Products in Portuguese and English

NOME COMERCIAL DO MEDICAMENTO	SUBSTÂNCIA ACTIVA	DOSAGEM	FORMA	APRESENTAÇÃO	FABRICANTE DO PRODUTO ACABADO	Nº DE REGISTO	DATA DA ÚLTIMA AUTORIZAÇÃO	EMPRESA
EVATOCIN	Oxitocina	5UI/ml	Solução injectável	2 carteiras de 5 ampolas de 1ml	Neon Laboratories Ltd - Índia	4087	18-3-2015	MEDÁFRICA, LDA
IZIOXYN	Oxitocina	5UI/ml	Solução injectável	10 ampolas de 1ml	BKRS Pharma PVT. Ltd - India	H5101	18-9-2017	EVEREADY PHARMA LDA
ARTETOCIN - 5	Oxitocina	5IU/ml	Solução injectável	10 ampolas de 1ml	Alchemy Medicine Pvt Ltd - India	H5927	12-11-2019	ARTEMIS PHARMACEUTICALS
ARTETOCIN - 10	Oxitocina	10IU/ml	Solução injectável	10 ampolas de 1ml	Alchemy Medicine Pvt Ltd - India	H5912	3-12-2019	ARTEMIS PHARMACEUTICALS
OXITOCINA INJECTAVEL BP	Oxitocina	10IU/ml	Solução injectável	10 ampolas de 1ml	Umedica Laboratories Pvt. Ltd - India	H6153	24-9-2020	MISSIONPHARMA MOÇAMBIQUE
KONTRAC -200	Misoprostol	200mcg	Comprimidos	1 blister de 2 comprimidos e	FOURRTS Laboratories LTD PVT-INDIA	1335	6-6-2019	GENERICS & SPECIALITIES, Lda
ISOVENT 200	Misoprostol	200mcg	Comprimidos	Embalagem de 1 blister de 10 comp	Square Pharmaceuticals Ltd- Bangaladesh	1118	16-8-2017	MAPUTO HEALTH CARE Lda
CYTOTEC	Misoprostol	200mcg	Comprimidos	Embalagem contendo 1 blister	NPIL Pharmaceuticals (uk)Ltd.	1604	31-8-2017	MEDIS FARMACÊUTICA, LDA
MISOFAR	Misoprostol	200mcg	Comprimidos	blister de 4 comprimidos	Industria Quimica e Farmaceutica VIR, S.A -	4703	6-10-2016	MEDIMPORT LDA
MISOFAR	Misoprostol	25mcg	Comprimidos	embalagem de 8 comprimidos	Industria Quimica e Farmaceutica VIR, S.A -	4704	6-10-2016	MEDIMPORT LDA
MISOTOL	Misoprostol	200mcg	Comprimidos	1 blister de 10 comprimidos	Biomatrix Healthcare Pvt Ltd - India	5027	29-6-2017	ACE HEALTH CARE LDA

MISTOP	Misoprostol	200mcg	Comprimidos	10 blister de 10 comprimidos	Dev Life corporation - India	G5366	30-7-2018	MDS - Medicamento e Diagnóstico na Saúde
MISOPROST 200	Misoprostol	200mcg	Comprimidos	1, 7 e 15 blister de 4 comprimdos	Cipla Lda, Goa Unit VIII - India	G5372	30-7-2018	WELL WORTH LDA
VIG MTP	Misoprostol	200mcg	Comprimidos	2 blister de 14 comprimidos	Kwality Pharmaceuticals - India	A5469	8-10-2018	FARMA HOLDING SA
KUSHI MISO	Misoprostol	200mcg	Comprimidos	10 blister de 12 comprimidos	Accent Pharmaceutical & Diagnostics - India	G5853	12-11-2019	SOCIEDADE AFRICANA DE SAÚDE LDA
AVERTISO	Misoprostol	200mcg	Comprimidos	10 blister de 4 comprimidos	ACME Formulation Pvt. Ltd - India	G5981	5-2-2020	MEDIMPORT LDA

Commercial Name	**Active substance**	**Dosage**	**Form**	**Presentation**	**Manufacturer**	**Registration number**	**Date of authorization**	**Enterprise**
EVATOCIN	Oxytocin	5UI/ml	Injectable solution	2 boxes of 5 1 mL ampoules	Neon Laboratories Ltd - Índia	4087	18-3-2015	MEDAFRICA, LDA
IZIOXYN	Oxytocin	5UI/ml	Injectable solution	10 1 mL ampoules	BKRS Pharma PVT. Ltd - India	H5101	18-9-2017	EVEREADY PHARMA LDA
ARTETOCIN - 5	Oxytocin	5IU/ml	Injectable solution	10 1 mL ampoules	Alchemy Medicine Pvt Ltd - India	H5927	12-11-2019	ARTEMIS PHARMACEUTICALS
ARTETOCIN - 10	Oxytocin	10IU/ml	Injectable solution	10 1 mL ampoules	Alchemy Medicine Pvt Ltd - India	H5912	3-12-2019	ARTEMIS PHARMACEUTICALS
OXITOCINA INJECTAVEL BP	Oxytocin	10IU/ml	Injectable solution	10 1 mL ampoules	Umedica Laboratories Pvt. Ltd - India	H6153	24-9-2020	MISSONPHARMA MOZAMBIQUE
KONTRAC -200	Misoprostol	200mcg	Tablet	1 blister pack of 2 tablets	FOURRTS Laboratories LTD PVT-INDIA	1335	6-6-2019	GENERICS & SPECIALITIES, Lda
ISOVENT 200	Misoprostol	200mcg	Tablet	1 blister pack of 10 tablets	Square Pharmaceuticals Ltd- Bangaladesh	1118	16-8-2017	MAPUTO HEALTH CARE Lda
CYTOTEC	Misoprostol	200mcg	Tablet	1 blister pack	NPIL Pharmaceuticals (uk)Ltd.	1604	31-8-2017	MEDIS FARMACEUTICS, LDA

MISOFAR	Misoprostol	200mcg	Tablet	1 blister pack of 4 tablets	Industria Quimica e Farmaceutica VIR, S.A -	4703	6-10-2016	MEDIMPORT LDA
MISOFAR	Misoprostol	25mcg	Tablet	Pack of 8 tablets	Industria Quimica e Farmaceutica VIR, S.A -	4704	6-10-2016	MEDIMPORT LDA
MISOTOL	Misoprostol	200mcg	Tablet	1 blister pack of 10 tablets	Biomatrix Healthcare Pvt Ltd - India	5027	29-6-2017	ACE HEALTH CARE LDA
MISTOP	Misoprostol	200mcg	Tablet	10 blister packs of 10 tablets	Dev Life corporation - India	G5366	30-7-2018	MDS - MEDICINES AND DIAGNOSTICS IN HEALTH
MISOPROST 200	Misoprostol	200mcg	Tablet	1, 7, and 15 blister packs of 4 tablets	Cipla Lda, Goa Unit VIII - India	G5372	30-7-2018	WELL WORTH LDA
VIG MTP	Misoprostol	200mcg	Tablet	2 blister packs of 14 tablets	Kwality Pharmaceuticals - India	A5469	8-10-2018	FARMA HOLDING SA
KUSHI MISO	Misoprostol	200mcg	Tablet	10 blister packs of 12 tablets	Accent Pharmaceutical & Diagnostics - India	G5853	12-11-2019	AFRICAN HEALTH SOCIETY LDA
AVERTISO	Misoprostol	200mcg	Tablet	10 blister packs of 4 tablets	ACME Formulation Pvt. Ltd - India	G5981	5-2-2020	MEDIMPORT LDA