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Research Article

Risk-Based Post-Marketing Surveillance (RB-PMS) of antimalarial drugs and maternal, neonatal and reproductive health (MNCH) in Mali

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Abstract

Objectives: In a world marked by the increase in chemoresistance leading to the adoption of therapeutic combinations, the advent of generic multi-source drugs, the spread of counterfeiting and substandard drugs, often without active ingredients or falsified active ingredients, a Greater vigilance by pharmaceutical regulatory authorities is needed. Drug Post-Marketing Surveillance (PMS) therefore plays an important role in detecting poor quality products on the market. Risk-Based Post-Marketing Surveillance (RB-PMS) is a new form of PMS that is emerging and was the subject of a recent WHO publication.

Methods: The survey covered certain regions and certain points of sale identified by a Technical Working Group. It aimed to assess the quality of antimalarial and MNCRH drugs available at certain risk distribution levels based on priority sites. The selection of drugs and geographic areas was made using risk-based sampling using the Drug Risk Assessment Tool (MedRS) developed by USP / PQM +.

Results: A total of 242 samples were taken and analyzed according to a risk-based protocol, of which 233 were compliant with a rate of 96% against 9 were non-compliant or 4% (P≤0,05). Non-compliant drugs were mainly from the public sector. We found 69% of the unregistered drugs that consisted mainly of antimalarial drugs and which came from India and China.

Conclusion: In view of the scarcity of resources and its scientific nature, this risk-based sampling and analysis technique (RB-PMS) must be pursued, optimized and made sustainable to ensure health and guarantee access to quality medicines for the health and well-being of populations.

Keywords: Antimalarials, MNCH, Quality Control, RB-PMS.

INTRODUCTION

Mali is a country where malaria is endemic in the Sahel zone of West Africa. Malaria control interventions have been dramatically scaled up over the past decade, resulting in a substantial decrease in parasite prevalence and possibly contributing to a significant drop in under-five mortality, all combined causes. Malaria transmission in Mali is highly seasonal, concentrated during and just after the rainy season (usually July to October), peaking in August and September. The incidence of malaria ranges from moderate to high in the southeast, where it is relatively humid, and decreases towards the north.[1,2]

Maternal and neonatal morbidity and mortality are high in countries in the West African region, including Mali. High mortality rates are associated with a combination of factors. They include delays in seeking health care among the population, long distances to travel to health facilities, leading to inaccessibility, limited access to safe and quality medicines, and delays in provision of care in health facilities. Maternal, Newborn and Child Medicines (RMNCH) are central to any strategy to effectively reduce morbidity and mortality in this population.[3] The quality of the drugs used is therefore essential and must be constantly monitored. The use of substandard and falsified medicines by patients can lead to treatment failure, prolong the treatment period, exacerbate patient suffering and lead to the development of resistance. In extreme cases, it can lead to death.[4]

Considering all the above and in a world marked by several challenges including, among others, the increase in drug resistance leading to the adoption of therapeutic combinations, the advent of multi-source generic drugs, the spread of counterfeiting and drugs under standard, often without active ingredients or active ingredients or falsified active ingredients, greater vigilance from the pharmaceutical regulatory authorities is necessary.[5]

To strengthen drug regulatory efforts in Mali, USP/PQM plus supports Mali's National Health Laboratory (LNS) in conducting risk-based post-marketing surveillance of circulating antimalarial and RMNCH drugs in the country. One of the activities of the 2020 work plan (PY1) is to implement a

survey to assess the quality of antimalarial and RMNCH drugs available at certain levels of distribution at risk according to priority sites in the country in order to determine the prevalence falsified and substandard medicines based on risk analysis (RB-PMS). RB-PMS is a new form of PMS different from conventional PMS. Based on risk, it is in the process of being put in place and was the subject of a recent publication by the WHO.[6]

MATERIAL AND METHODS

Scope and Duration of the Survey: The survey covered certain regions and certain points of sale identified by the Technical Working Group, which are: (Health Center sales depots, Districts Distributor, hospital and private pharmacies, Popular Pharmacy of Mali, illegal points of sale) from October 2020 to January 2021. The priority regions/sites selected on the basis of risk criteria for the collection of samples are the following: Kayes, Koulikoro, Sikasso, Ségou. Samples were taken at different levels of the drug distribution chain.

Level 1: Market entry points: eg importers/manufacturers warehouse, central and regional medical stores. NGO central stores, procurement centers or other facilities supplied directly under various programs.

Level II: Regulated Retailers: For example, wholesalers and other regulated retailers.

Level III: Regulated dispensaries: retail pharmacies, hospitals, health centers, secondary health centers, district hospitals, clinics, maternities, community health workers, treatment centers.

Level IV: Illegal outlets that sell drugs outside the licensed distribution system. Includes the informal or unauthorized market (open market, stalls and itinerant drug sellers).

Sélection des médicaments et zones géographiques

The selection of drugs for this quality survey was based on the purpose of the survey and the potential public health impact using a series of risk factors. The Drug Risk Assessment Tool (MedRS) was developed by USP/PQM Plus.[7]

The following risk factors were considered:

- Drug stability
- GMP compliance (from manufacturers, if known)
- Complexity of the distribution chain
- Degree of exposure of the population
- Patient vulnerability
- Complexity of dosage form
- Therapeutic risk
- Degree of harm due to poor quality
- Availability of the drug during the survey period

This tool allowed us to identify the following drugs as drugs of interest based on the risk analysis of drugs according to the guideline for the implementation of risk-based post-marketing quality surveillance in low- and middle-income countries (LMIC).[8]

Table 1: List of drugs to be covered in the RB-PMS

N⁰	Antimalarial drugs	SRMNI drugs
1	Artesunate injection	Oxytocine injection
2	Artemether + Lumefantrine tablets	Diazepam injection
3	Quinine injection	Amoxicilline dispersible tablet
4	Artemether injection	Medroxyprogesterone acetate injection (IM)

Sample analysis in the laboratory

Sample analysis was performed in stages using a risk-based testing approach, in accordance with the document Guidance for Implementing Risk-Based Post-Marketing Quality Surveillance in Low-Income Countries and intermediate, which is detailed in the following table [6].

Table 2: Proportion of tests on the samples according to the three test levels

Test	Scope of testing	Specification
Level 1: Visual and physical inspection	All samples collected must be visually inspected to determine registration and packaging integrity, in the field, at the time of collection	Pharmacopoeia or registration dossier (manufacturer's requirement)
Level 1: Labeling		
Level 2: Identification (CCM)	Level 1 compliant samples are further checked at Level 2	Minilab technique
Level 2: Disintegration test		
Level 3: Compendial Tests	- 20% of samples compliant with level 2 - 100% of non-compliant with levels 1 and 2	Monograph of the relevant pharmacopoeia

Any sample that failed a test was examined according to LNS Out of Specification (OOS) procedures. Once the result is confirmed, it is not necessary to continue analyzing the sample until the next test.

RESULTS

Situation of the samples taken

A total of 262 samples were taken from 4 geographical regions (Table 3) at the 4 levels of the drug distribution chain described in the methodology.

Table 3: Situation of samples taken by region

Regions	Antimalarials	SRMNI	Total
Kayes	42	33	75
Koulikoro	61	NA	61
Sikasso	29	29	58
Segou	68	NA	68
Totals	**200**	**62**	**262**

Manufacturers and products collected

A large majority of products came from India (34%) followed by China (30%).

We also noticed that a large part of the products (27%) was of unknown origin.

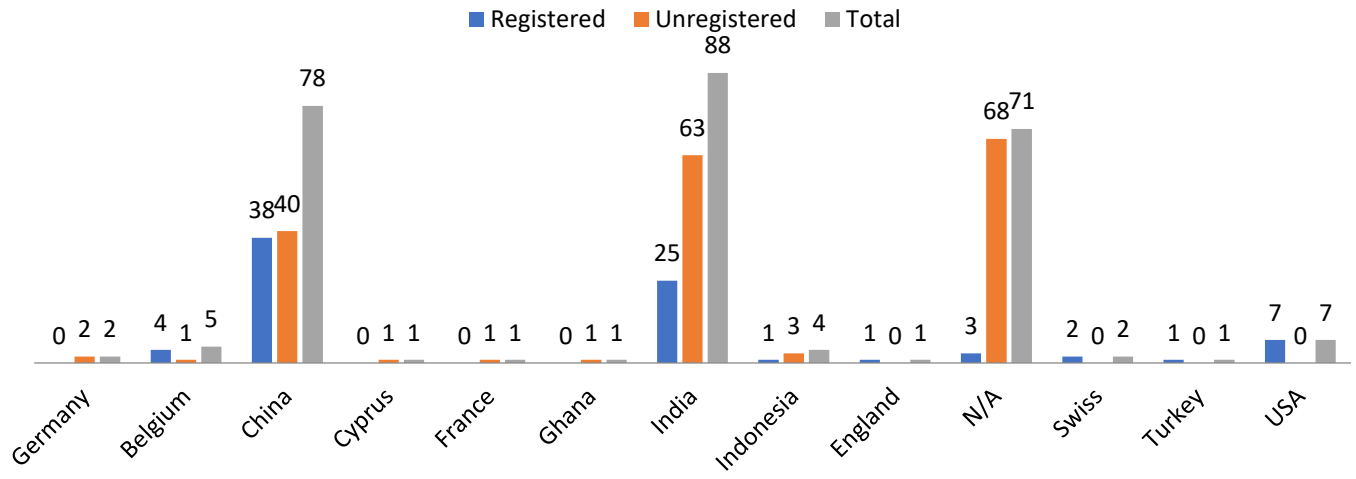

Figure 1: Situation of unregistered products by origin.

Samples registration status

Only 31% of the medicines collected were registered.

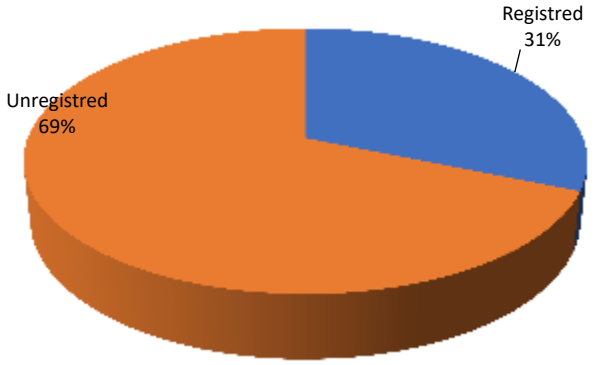

Figure 2: General registration status of the products.

Products registration status by active ingredient

Antimalarials were the least registered drugs with a rate of 40% for Artemether + Lumefantrine, followed by Artemether injectaion (34%) and Quinine injection (33%).

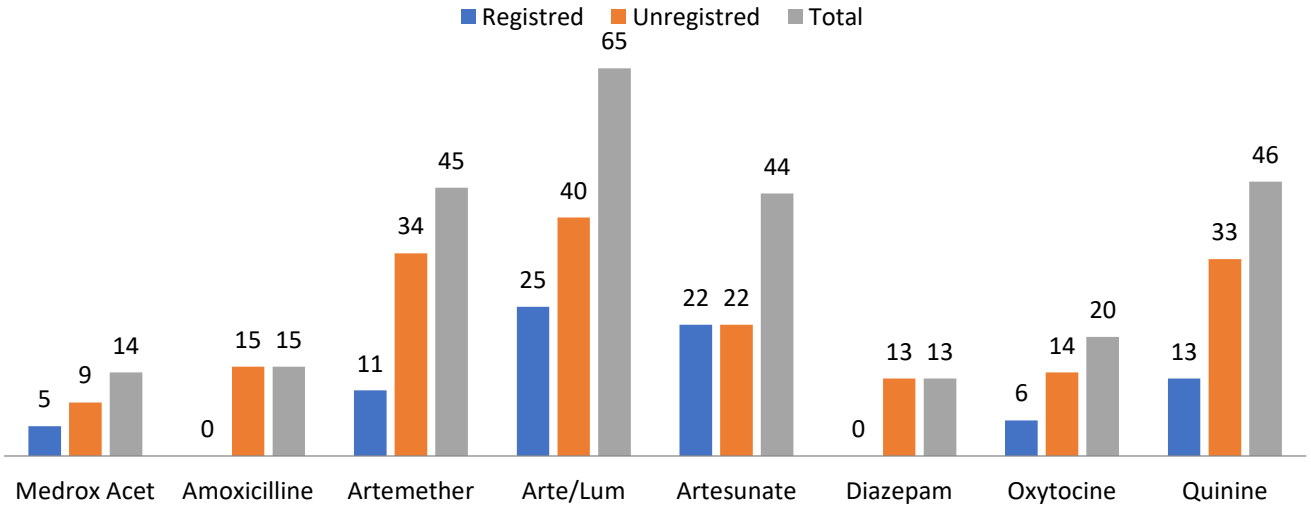

Figure 3: Product registration status by active ingredient.

Situation of products by molecules

Artemether + Lumefantrine was the most represented active ingredient with 25% followed by Quinine injection, Artemether injection and Artesunate injection with 17% each.

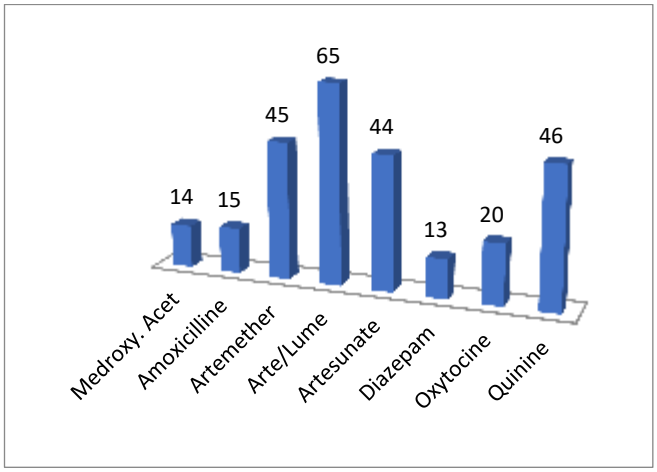

Figure 4: Situation of products by molecules.

Compliance with Specifications

Global Results

Out of 242 samples tested, 233 were compliant, i.e. a rate of 96% and 9 non-compliant, corresponding to a rate of 4%.

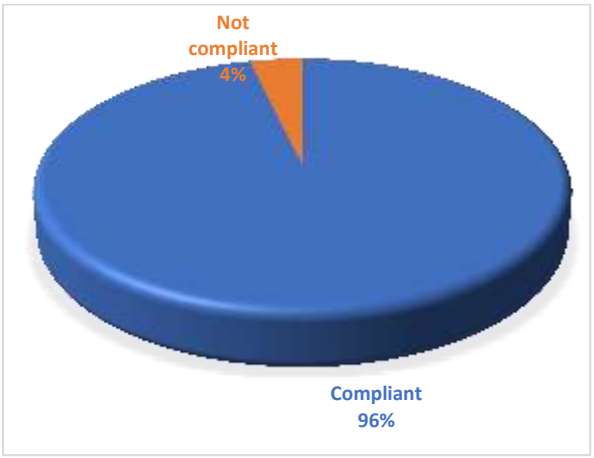

Figure 5: Global situation of products according to compliance

Level III confirmation test

According to the protocol, 20% of the samples that passed the Levels I and II tests in addition to all the samples that failed were tested at Level III.

Table 4: Level III quality testing results.

Products name	Number	20%	Non Compliant
Artesunate injection	43	8	1
Artemether + Lumefantrine tablets	62	16	7
Quinine injection	45	9	0
Artemether injection	44	9	0
Total	**194**	**42**	**8**

Thus 42 samples (Table above) plus the 7 previous non-compliant samples, i.e. a total of 49 samples were tested at this level. Among the 49 samples, this level III revealed 8 cases of non-compliance, including the 7 plus 1 other case of under-dosage of active ingredient.

In addition, the RMNI samples were all tested at this level (because of the unavailability of Minilab techniques allowing them to be tested at level II) except for the Diazepam samples for unavailability of the reference substance. Thus, 48 samples were analyzed, of which 1 proved to be non-compliant.

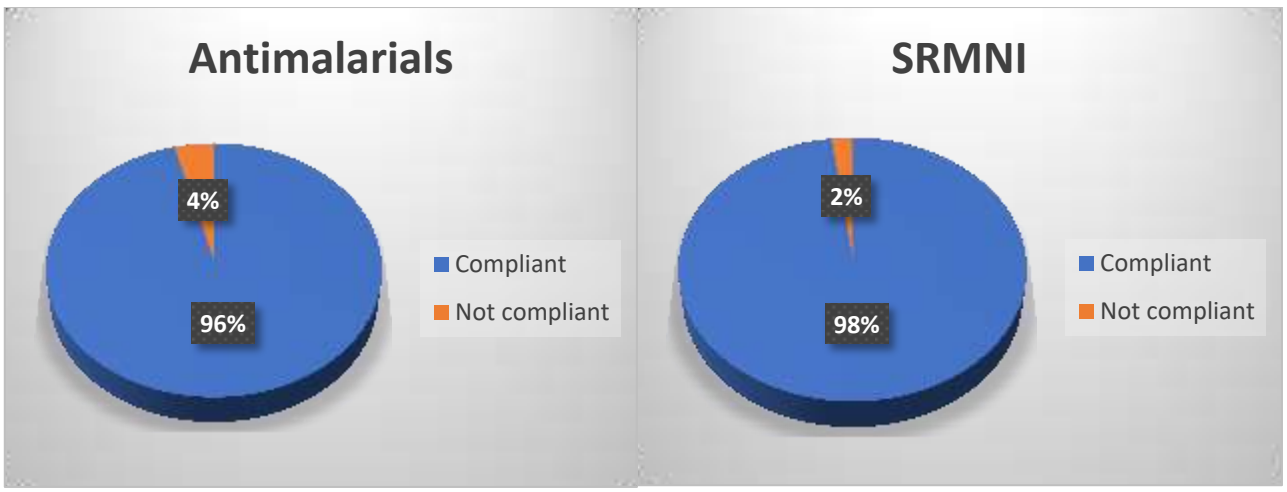

Figure 6: Level III quality test results.

DISCUSSION

Test methods and data quality

In accordance with the Guidance document for implementing risk-based post-marketing quality surveillance in low- and middle-income countries, which is detailed in Table 1, we conducted sample analysis by step using a risk-based testing approach that is done in 3 levels. Non-compliant samples were subject to OOS processing in accordance with procedure POS-014-01 in its chapter 6.2.1 which describes out-of-specification results and INS-021-01 which describes the management of out-of-specification results. The procedure says that any OOS result must be reported to the head of the Laboratory who initiates the OOS procedure in collaboration with the Quality Assurance manager. The procedure describes the OOS management steps up to the writing of the final report confirming the first result. All data has been submitted for review and approval by the laboratory's quality control functions in accordance with our procedure POS-011-01, Procedure for the control of technical records, which in its chapter 6.4 describes the provisions specific to the certificate. analysis and controls required before final approval.

Results interpretation

Among the cases of non-compliance encountered, 8 were antimalarials (7 Artemether + Lumefantrine and 1 Artesunate) and 1 RMNI (Medroxyprogesterone Acetate) drugs. The regions of Koulikoro and Sikasso had the highest numbers with 4 and 3 products respectively and the public sector accounts for 90% of the products. These results confirm those of Sidibé et al who found that 87.7% came from the public sector and 12.3% from the private sector.[9]

In this study, a large majority of the products came from India (34%) followed by China (30%). These results confirm those of Sidibé et al who found 45% and 17% for India and China respectively.[9]

This study found that almost all products of unknown origin (96%) were unregistered. This difference is explained by the fact that some of these products were registered. They are followed by India and China with 63% and 40% respectively

CONCLUSION:

In view of the scarcity of resources, this risk-based sampling and analysis technique (RB-PMS) must be continued, optimized and sustained to ensure health and guarantee access to quality medicines for health and the well-being of populations.

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- USAID/PMI and technical support from USP/PQM plus

Conflicts of Interest: None

REFERENCES

1. World malaria report 2019 [Internet]. [cité 30 déc 2021]. Disponible sur: https://www.who.int/publications-detail-redirect/9789241565721
2. Mali [Internet]. Severe Malaria Observatory. [cité 30 déc 2021]. Disponible sur: https://www.severemalaria.org/fr/pays/mali
3. Demographic and Health Survey in Mali 2018.pdf
4. WHO | WHO Global Surveillance and Monitoring System [Internet]. WHO. [cité 27 nov 2020]. Disponible sur: http://www.who.int/medicines/regulation/ssffc/surveillance/en/
5. Handbook_of_training_materials_SF_French.pdf [Internet]. [cité 30 déc 2021]. Disponible sur: https://www.who.int/medicines/regulation/ssffc/mechanism/Handbook_of_training_materials_SF_French.pdf
6. Pitts A. Guidance for Implementing Risk-based Post-marketing Quality Surveillance in Low- and Middle-income Countries. :54.
7. MedRS | Log In [Internet]. [cité 29 déc 2021]. Disponible sur: https://medrsv2.com/
8. Drug Quality Promotion Program. Strengthening National Capacity in Medicine Quality: Five-Year Summary (2005-2009) of the Medicine Quality Promotion Program in Southeast Asia and the Philippines. Rockville, Md: The United States Pharmacopoeial Convention. Accessed: 09 Nov. 2018. Available at: http://www.usp-pqm.org/sites/default/files/pqms/article/rdmareport.pdf
9. A Sidibé O. Quality control of medicines antimalarials in seven (07) administratives regions of mali and Bamako district: operationalization of minilab kits. Published online 2012. Accessed December 23, 2021. https://www.bibliosante.ml/handle/123456789/1856