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Risk-Based Post-Marketing Surveillance (RB-PMS2) of Antimalarial and MNCH drugs in Mali (PY2)

Ousmane DEMBELE[1,2], Patomo Dominique Arama[1], Seydou Moussa Coulibaly[2], Jacques Dakouo[2], Nana Houmama Cissé[2], Benoît Yaranga Koumaré[1,2].

[1]Faculté de Pharmacie de Bamako, Université des Sciences, des Techniques et des Technologies de Bamako, Mali.

[2]Laboratoire National de la Santé du Mali.

ABSTRACT

Background and Objectives: The advent of multi-source generic drugs has exacerbated the prevalence of drugs and the spread of counterfeit and sub-standard drugs requiring increased vigilance and collaboration from drug regulatory authorities. Post-marketing surveillance (PMS) of medicines therefore plays an important role in detecting poor quality products on the market. Risk-Based Post-Market Surveillance (RB-PMS) RB-PMS helps optimize resource utilization and create sustainable post-market surveillance programs that are integrated and implemented as a key regulatory function.

Methods: The survey concerned points of sale identified by a Technical Working Group in certain geographical areas according to risk-based approaches applied in the selection of the type of drugs to be targeted. It took place from September to December 2021 and aimed to assess the quality of antimalarial and MNCH medicines.

Results: A total of 320 samples were taken and analyzed according to a risk-based protocol, of which 306 were compliant with a rate of 96% against 14 were non-compliant or 4% (P≤0,05). Non-compliant drugs were from both the public and private sectors. We found that 84% of drugs were unregistered among which antimalarials were the least registered drugs with a rate of 66% against 34% for MNCH drugs and came mainly from India and China.

Conclusion: The RB-PMS allows the optimization of health resources in LMIC. In view of its scientific nature, this sampling and analysis technique must be made permanent to ensure health and guarantee access to quality medicines for the health and well-being of populations.

KEYWORDS: Antimalarials, MNCH, quality control, RB-PMS.

ARTICLE DETAILS

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INTRODUCTION

Malaria remains a major public health problem worldwide. The World Health Organization report (WHO 2021) estimates the number of malaria cases at 241 million with 627,000 deaths. In Mali, malaria is a real public health problem and represents 37.51% the first reason for consultation among which children under 5 and pregnant women are the most vulnerable groups. The management of malaria cases (curative and preventive treatment), prevention of malaria in pregnant women, chemoprevention of seasonal malaria in children aged 3 to 59 months is done by antimalarial drugs.(1,2)

Maternal and neonatal morbidity and mortality are high in countries in the West African region, including Mali where maternal and neonatal mortality remains high, with 325 maternal deaths per 100,000 live births and 33 neonatal deaths per 1,000 live births. High mortality rates may be associated with limited access to safe, quality medicines.

For adequate management of these diseases, the quality of the drugs used is therefore essential and requires constant monitoring. The use of substandard and falsified medicines by patients can lead to treatment failure and promote resistance and even lead to death.(3,4)

With the advent of multi-source generic drugs and the spread of counterfeit and substandard drugs, pharmaceutical regulatory authorities must be more vigilant.(5)

In its activities, a TWG has been set up to conduct periodic surveys to assess the quality of antimalarial and MNCH drugs available in the country in order to determine the prevalence of falsified and substandard drugs based on an analysis of risks (RB-PMS). It is extremely difficult and often impossible to fully regulate the quality of all medicines circulating in the country. It is therefore imperative to apply risk-based approaches to select drugs for sampling and testing in a post-marketing surveillance program. RB-PMS is a new form of PMS that is different from conventional PMS, based on risk, it is being implemented in many African countries.(6)

MATERIAL AND METHODS

Scope and Duration of the Survey: The survey concerned points of sale identified by a Technical Working Group in certain geographical areas according to risk-based approaches applied in the selection of the type of drugs to be targeted. It took place from September to December 2021 at public and private medicine outlets in the following regions and priority areas: Bamako, Kayes, Koulikoro, Sikasso, Segou. Samples were taken at some levels of the drug distribution chain.(6)

Selection of drugs and geographical areas

Drugs were selected based on risk analysis using a series of risk factors through the Drug Risk Assessment Tool (MedRS) developed by USP/PQM Plus (7). This tool helps to identify medicines based on risk analysis according to the guideline for the implementation of risk-based post-marketing surveillance in (LMIC).(8)

Table 1: Drugs to be covered in the survey

N⁰	Antimalarials	MNCH
1	Artesunate injection	Oxytocine injection
2	Artemether + Lumefantrine tablets	Diazepam injection
3	Quinine injection	Magnesium Sulfate injection
4	Artemether injection	

Sample analysis in the laboratory

Sample analysis was performed using a risk-based 3-step testing approach in accordance with the document Guidance for Implementing Risk-Based Post-Marketing Surveillance in LMICs (6). It is based on the use of three levels of drug quality assessment, using methodologies different from each other, increasing complexity and complementary to each other:

Level 1: Visual and physical inspection

- Labeling and packaging
- Appearance, conditions and physical characteristics of the drug

Level 2: Basic analytical tests

- Disintegration:
- Physical process required for dissolution of solid dosage forms
- Thin Layer Chromatography (TLC)
- Identification of the active pharmaceutical ingredient (API)
- Presence of impurities
- Semi-quantitative assessment of content (20% range)

Level 3: pharmacy/validated tests

- According to recording specifications
- Assessment of all critical quality attributes

RESULTS

Samples situation

320 samples were collected from 5 geographical areas (Table 2) at some levels of the drug distribution chain described in the methodology.

Table 2: Proportion of samples by region

Regions	Antimalarials	MNCH	Total
Bamako	34	16	50
Kayes	36	21	57
Koulikoro	69	14	83
Sikasso	41	29	70
Segou	45	15	60
Totals	**225**	**95**	**320**

Situation of products collected according to the manufacturer

Most of the products came from India (47%) followed very closely by China (45%). This confirms the results obtained by PMS1 who found 34% and 30% respectively for India and China (9).

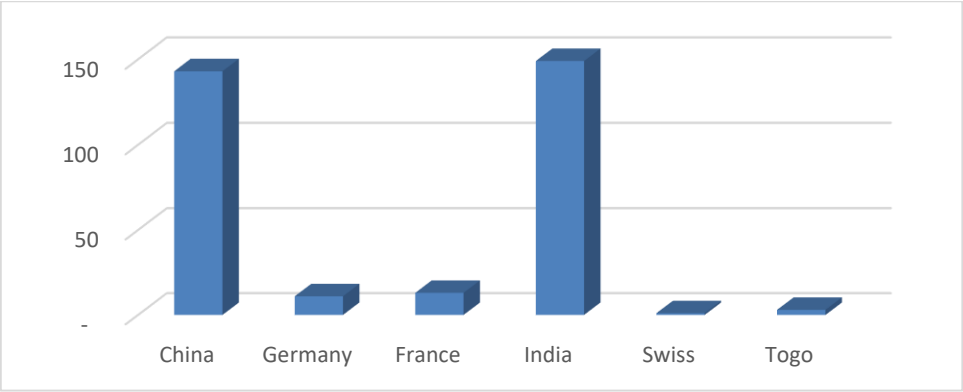

Figure 1: Situation products by manufacturer.

Almost all of the products from China (74.8%) and India (74.5%) constituting 92% of the samples were unregistered.

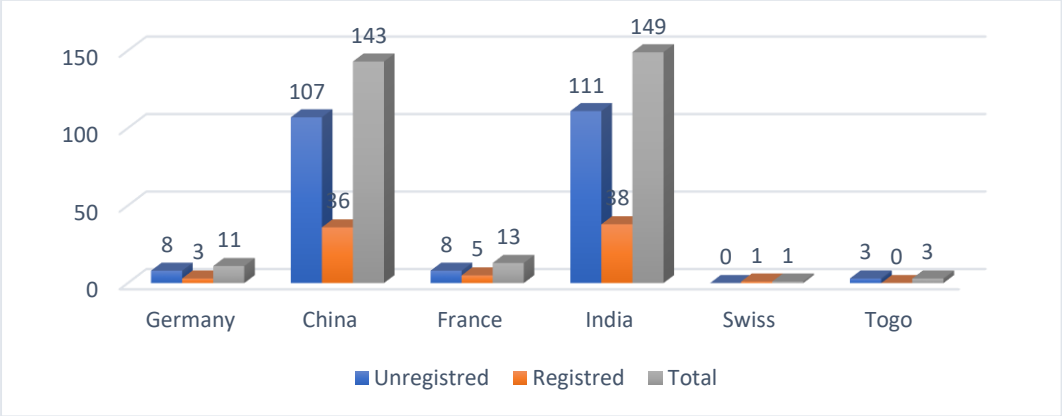

Figure 2: Situation of unregistered products by origin.

Samples registration status

In this work, only 26% of drugs were registered in contrast to PMS1 which was 31% (10).

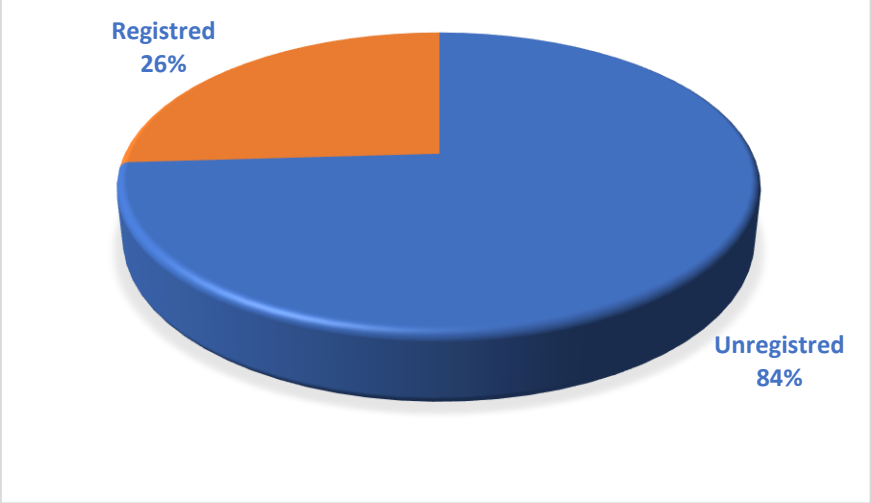

Figure 3: General registration status of the products.

Products registration status by active pharmaceutical ingredient

Antimalarials were the least registered drugs with a rate of 66% against 34% for MNCH drugs. Among the antimalarials, injectable Artemether (40%) followed by injectable Quinine (30%) were the least registered. For MNCH drugs, all Diazepam and Magnesium Sulfate samples were unregistered.

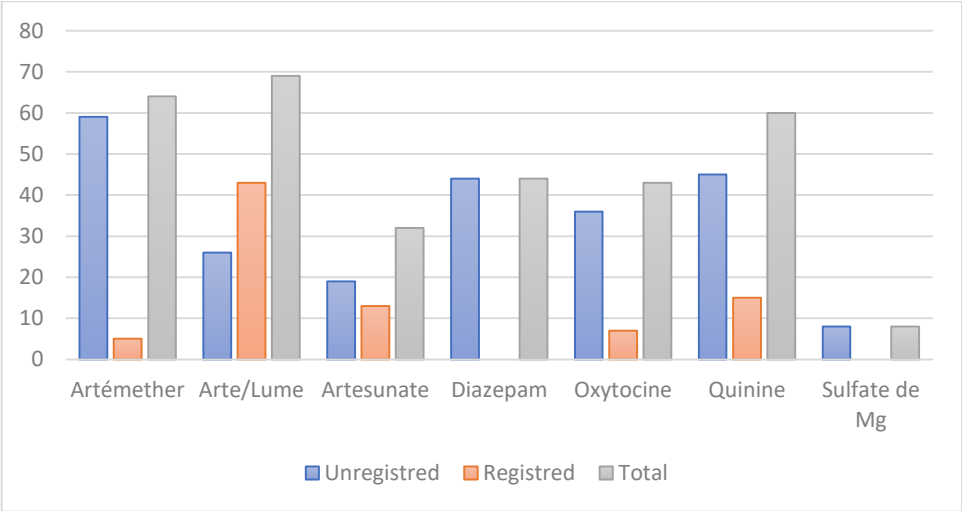

Figure 4: Product registration status by active pharmaceutical ingredient.

Situation of products by active pharmaceutical ingredient

Artemether + Lumefantrine was the most represented active ingredient with 22% followed by Artemether injection 20% and Quinine injection 19%.

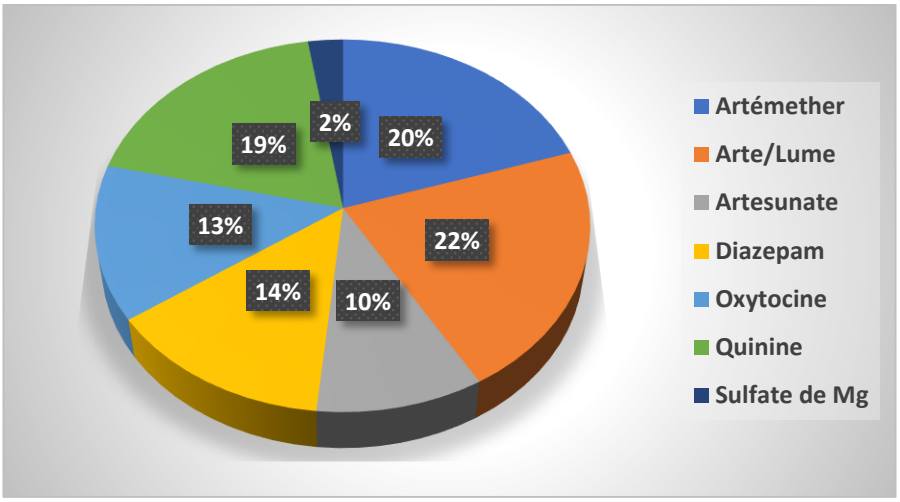

Figure 5: Situation of products by active pharmaceutical ingredient.

Compliance with Specifications

Global Results

Out of 320 samples tested, 306 were compliant, i.e. a rate of 96% and 14 non-compliant, corresponding to a rate of 4%.

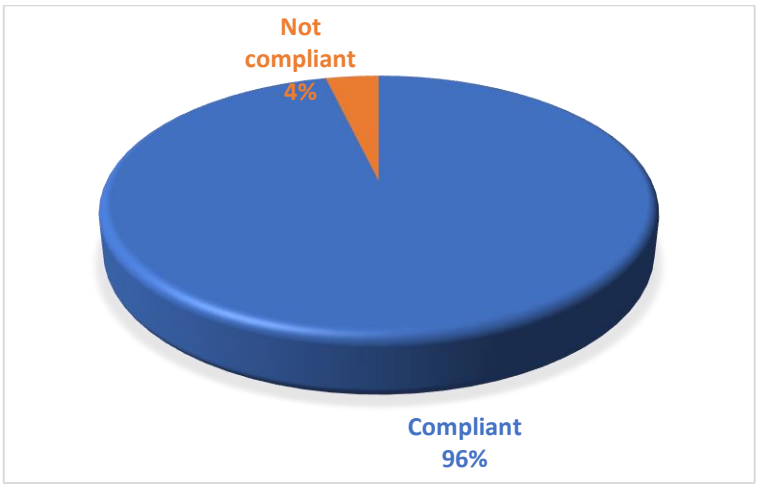

Figure 6: Global situation of products according to compliance

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	32	7	0
Artemether+Luméfantrine tablet	69	18	2
Quinine HCl injection	60	12	0
Artemether injection	64	14	0
Diazepam injection	44	12	12
Total		**63**	**14**

Thus 63 samples (Table above) plus the 14 previous non-compliant samples, i.e. a total of 77 samples were tested at this level. Among the 77 samples, this level III revealed and confirmed 14 cases of non-compliance, i.e. the 14 non-compliant samples of level II.

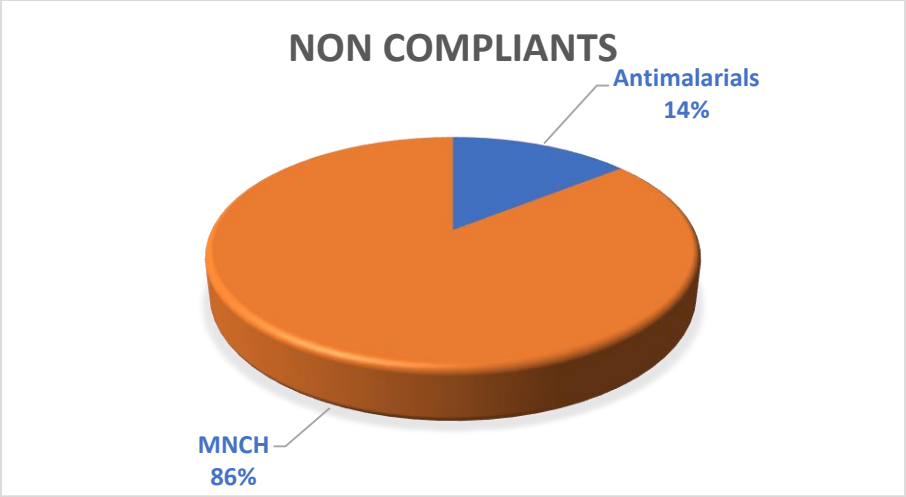

Figure 7: Level III quality test results.

Among the cases of non-compliance encountered, 2 were antimalarials (Artemether + Lumefantrine) and 12 were MNCH drugs (Diazepam). The region of Kayes had the highest number with respectively 4 samples for the public sector and 3 for the private sector.

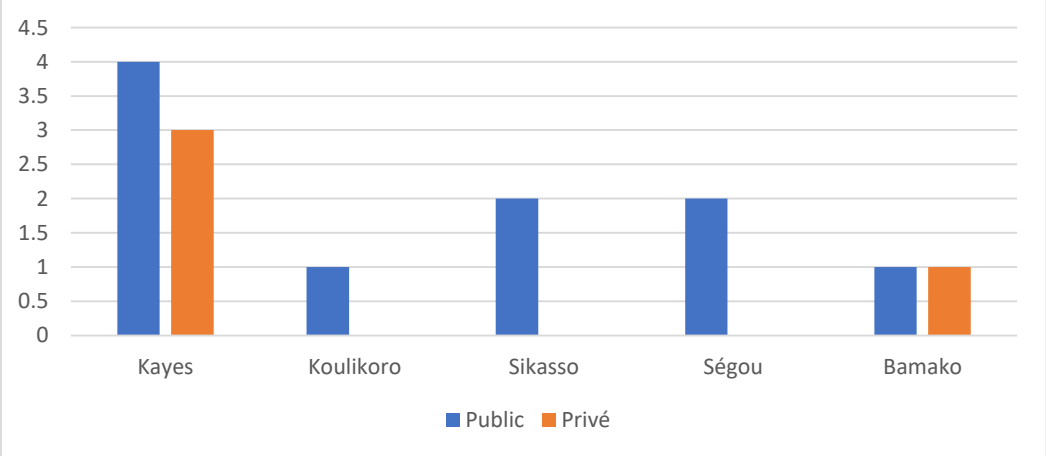

Figure 8 : Situation of non-conformities by sector and by region.

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, 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 LNS's procedure. All data has been submitted for review and approval by the laboratory's quality control functions and a certificate of analysis was issued for each sample.

Results interprétation

Out of 320 samples tested, 306 were compliant, i.e. a rate of 96% and 14 non-compliant, corresponding to a rate of 4%. These results confirm those of Dembélé et al who also found 4% non-compliance (11). Among the cases of non-compliance encountered, 2 were antimalarials (Artemether + Lumefantrine) and 12 MNCH (Diazepam) drugs. The causes of non-compliance were due to an absence of active ingredient (API). The region of Kayes had the highest number with respectively 4 samples for the public sector and 3 for the private sector. The public sector accounts for 71% 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.(12)

We found that a large majority of products came from India (47%) followed very closely by China (45%). These results confirm those of Dembélé et al who found 34% and 30% respectively for India and China(9).

Only 26% of the medicines collected were registered in contrast to PMS1 which was 31% (10). Antimalarials were the least registered drugs with a rate of 66% against 34% for MNCH drugs. Among the antimalarials, injectable Artemether (40%) followed by injectable Quinine (30%) were the least registered. For MNCH drugs, all Diazepam and Magnesium Sulfate samples were unregistered.

CONCLUSION

Using a risk-based approach in developing the study protocol, collecting samples, and analyzing samples through the three-tiered approach can reduce the number of samples that should be tested using pharmacopoeial methods and can therefore reduce the costs associated with conducting sampling and analysis activities. This study allowed us to detect 14 non-compliant products that were withdrawn from the market and regulatory measures were taken to ensure health and guarantee access to quality medicines for health and the well-being of populations.

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- The National Institute of Public Health, the People's Pharmacy of Mali,
- The National Program for the Fight against Malaria, the Sectoral Unit for the Fight against AIDS, Tuberculosis and Hepatitis,
- The National Council of the Order of Pharmacists,
- The Union of Private Wholesalers of Mali.
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Conflicts of Interest: No conflict of interest.

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