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Original article

A Machine Learning Model for Assessing the Prevalence of Counterfeit Antimalarial in Geographical Zones of Nigeria

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Abstract

Introduction: Antimalarial is listed among the most common type of live saving medicines that are counterfeited. In Nigeria counterfeited antimalarial continue to pose a great threat to the health of the citizens and there is the need to assess its incidence within the country's six zones. This study assessed the prevalence of counterfeited antimalarial within the six geographical zones of Nigeria and the impact of zones on counterfeiting using a machine learning model for classification. ***Methodology:*** Secondary data on 2442 antimalarial collected from all the states in Nigeria were grouped based on geographical zones. The medicines were tested for originality using the gold approach for detection of counterfeit medicine; the Standard Scientific Laboratory (SSL) Data was separated to 70% training and 30% testing and 10- fold Cross Validation (CV) was performed. The training set was used to derive the models while the test set was used to evaluate the performance of the models. Three varieties of the training data were generated using the Synthetic Minority Oversampling Technique (SMOTE). This was done to ensure a more accurate prediction and a better model performance. Binary Logistic Regression (BLR) models were thereafter fitted to the training data and the three varieties of its resampling. The four models namely M1, M2, M3 and M4 were fitted with data containing 33%, 40%, 45% and 50% of the counterfeited antimalarial class respectively. The performance of the four fitted models were assessed with metrics like sensitivity, specificity and model accuracy. ***Results:*** The results showed that there is a higher incidence of counterfeited antimalarial in the north-east and south-east zones than in the other four zones of Nigeria. The work also revealed model accuracies of 67%, 65.8%, 65.8% and 56,8% for M1, M2, M3 and M4 respectively. M1 was biased as it did not correctly predict any counterfeited antimalarial. M2 and M3 performed better than M4 in terms of model accuracy and specificity while M4 performed better only in terms of model sensitivity. ***Conclusion:*** Overall, only 66% of antimalarial was correctly predicted by the best performing model. This suggest that zone alone is not adequate to classify or predict originality/counterfeiting status of Antimalarial in Nigeria.

Keywords: ***Antimalarial, model accuracy sensitivity, geographical zones, resampling.***

Introduction

Nigeria's healthcare system is under varying attack. In addition to frequent diseases outbreak, exodus of many medical professional and pharmaceutical giants, heavy reliant on imported medicines and very expensive healthcare delivery system, the influx of fake and substandard medicines has become a major challenge causing pain to unsuspecting members of the public [1]. Counterfeited medicines are definitely deepening the despair of the Nigerian people who require quality medicines to treat many diseases plaguing them. According to the office of drugs and crime of the United Nation, counterfeit medicines is responsible for the death of about five hundred thousand people in sub-Saharan Africa each year [2]. The prevalence of counterfeited medications in Nigeria has been ascribed to inadequacy in medicines regulation along with lack of access to quality medicines in the healthcare delivery system [3]. Another factor that opens the way for counterfeit medicines perpetrators in Nigeria is the porosity at the different levels of the pharmaceutical supply chain [4]. Medicines are sold in kiosks, stalls and street corners in highly unregulated open markets across major cities in Nigeria. [5]. These unregulated open markets that include Sabon-Gari market in Kano, Idumota market in Lagos and the head-bridge markets in Onitsha have become the channels and sources of counterfeit medicines in Nigeria and other sub-Saharan nations [5]. It is shocking that these markets are main sources of medicines to several hospitals, wholesalers, retailers and licensed pharmaceutical shops despite the fact that the Nigerian government launched guidelines for medicines distribution in the country [6]. These markets should be rip to shreds instantly because if they continue to be operational, accomplishing a sustainable decrease in the circulation of counterfeit medicines in Nigeria, and possibly sub-Saharan Africa, will be a tough task [7].

Counterfeited medicine comprises those that are mislabeled fraudulently in relation to composition identity and source This description includes fully fake medicines, those tampered with, diluted, adulterated and repackaged so as to alter the dosage, source,

or expiration date [8]. Substandard medicines that are cheaply produced in order to make unlawful profits also constitute counterfeit medicines. Although. the National Agency for Food and Drug Administration and Control (NAFDAC) reported a decrease in the percentage of circulating counterfeit medicine from 40% in 2001 to 16.7% in 2015 [9], the problem remains a major challenge [10]. For instance, NAFDAC reported in 2018 that fake foods and medicines worth over 10 million US dollars were destroyed in the country [11]. yet the complexity in the circulation of counterfeit drugs means that this issue continues to pose significant risk to the Nation's healthcare system.

Medicines such as antimalarial which are of public health importance are more targeted for counterfeiting [10]. The counterfeit of antimalarial medicines did not initially receive enough attention compared with significant efforts made in other area of malaria control According to [12], antimalarial is listed among the most common type of live saving medicines that are counterfeited. The World Health Organization (WHO) reported in 2021 of 68 million cases of malaria in Nigeria and about 194000 resultant deaths [13]. It was also reported that one quarter of the deaths from the disease can be attributed to counterfeited antimalarial [14]. Counterfeiting has been shown to be a contributing factor to resistance of chloroquine and sulphadoxine-pyrimethamine to malaria parasites in Nigeria [15]. Currently, Artemisinin-based Combination therapies (ACT) are the recommended treatment for malaria in the country and because of their effectiveness and widespread use, they are now the target of criminals for counterfeiting. ACTs are mainly produced in Asia with possibly over 200 million courses used annually in Africa [16]. The demand and cost implication of ACT provide the enabling environment for the trafficking of fake artemisinin [16]. Counterfeiting medicines such as antimalarial is more than a criminal act. Some authors such as [17] described the act as manslaughter because these crooks make pills out of commodities such as chalk, starch and a variety of erroneous active ingredients. They target poor people that are mostly affected by deadly disease such as malaria and who cannot afford quality medicines. These perpetrators completely understands that their ineffective medicines can kill people who could have otherwise survived the disease. [16]. There are no therapeutic or sub-therapeutic quantities of artemisinin derivatives in fake antimalarial. It has been reported that these fake antimalarial sometimes contain potentially unsafe substance such as metamizole, melamine or safrole [16]. Clearly, counterfeited antimalarial is one of the biggest public health challenges in Nigeria and sub-Saharan region [16] and there is a need to find ways of tackling this menace.

In tacking the trade in counterfeiting medicines like antimalarial, it is important to know the gravity of the issue and to be able to determine or predict the way these syndicates distribute fake medicines within the country. According to [16], the precise figures of counterfeit medicines in rural areas of Africa is lacking. Recently, the federal house of representatives directed its committee on HIV/AIDS, tuberculosis and malaria control to carry out a baseline survey across the six geo-political zones of the country on fake anti-malaria medicines, the survey was intended to provide useful information in the fight against counterfeited antimalarial. However, since 2012, NAFDAC has embarked on continuous nationwide survey on counterfeit medicines. Samples of medicines are being collected across all states and the federal capital territory in Nigeria and tested for counterfeiting in a Standard Scientific Laboratory (SSL). The SSL is the gold approach to detection of counterfeit medicine. This study used data generated from the survey to determine the prevalence of counterfeited antimalarial each of the six zones of Nigeria. A machine learning model for classification was used to assess the extent to which the zone an antimalarial was sampled from can be used to predicts its originality/counterfeit status.

Materials and Methods

Study Design

Multi-stage sampling technique was used to randomly select antimalarial medicines from ten drug outlets within each state in Nigeria. Selected medicines were later tested for originality using the gold approach for detection of counterfeit medicine which is the SSL test.

The following encoding in equation (1) was used for the response variable (SSL results) and the predictor variable (zone where antimalarial are sampled from).

$$Y = \begin{cases} 0, Fail \\ 1, Pass \end{cases}$$

$$X = \begin{cases} 0, Otherwise \\ 1, if\ medicine\ was\ sampled\ from\ a\ particular\ zone \end{cases} \quad (1)$$

Data were separated into training and testing sets as typically done in machine learning methodology. The training set was used to derive the model while the test set was used to evaluate the performance of the model. Typically, data are separated into 80% training and 20% testing or 70% training and 30% testing. In this work, the models were built using 70% (1710) of the entire data set (2442) as training data and 30% (732) as testing data.

Cross Validation

In other to reduce the test error rate, k-fold Cross Validation (CV) was performed on the training set. CV for classification problem uses the number of misclassified observations to quantify the test error. Mathematically CV as given by [18] is shown below in equation (2)

$$CV = \frac{1}{k}\sum_{i=1}^{k} Err_i \quad (2)$$

where $Err_i = I(y_i \neq \hat{y}_i)$

In this work, k was chosen to be equal to ten i.e. $k = 10$ and the resultant model accuracy after CV is referred to as CV model accuracy.

Statistical Methodology

The machine learning model for classification used in this work is the Binary Logistics Regression (BLR) The methodology of BLR as described by [19] is explained below.

From the general linear model in (3)

$$Y = X\beta + \epsilon \quad (3)$$

Where, Y is a vector of responses, X is $n \times p$ model matrix, β is a $p \times 1$ vector of parameters and ϵ is the random error terms

The estimated model given a vector of predictors $X = X_1, X_2 \ldots X_p$ is given in equation (4)

$$Y = E(Y/X) = X\beta \quad (4)$$

Transforming to positive values by taking the exponential result into equation (5)

$$\exp(Y) = \exp(X\beta) \quad (5)$$

Also changing (5) to probabilities result into equation (6)

$$P(Y/X) = p = \frac{\exp(Y)}{1+(\exp(Y)} \quad (6)$$

(6) is the probability of success, the probability of failure is as shown in equation (7)

$$1 - p = 1 - \frac{\exp(Y)}{1+\exp(Y)} \quad (7)$$

The odd is equal to $\exp(Y)$ and the logit is given in equation (8)

$$In\left(\frac{p}{1-p}\right) = X\beta \quad (8)$$

Estimation of Parameters

The parameter of the logistics model in (6) are estimated using the Maximum Likelihood Estimator (MLE). The response of the logistic regression model is distributed as a Bernoulli: $Y \sim Ber(p)$ and its likelihood function is

$$L = p^{\sum Y}[1-p]^{n-\sum Y}$$

$$L = \sum Y\ In\ p + n - \sum Y\ In\ (1-p) \quad (9)$$

Differentiating equation (9) with respect to the parameter β and equating to zero gives (10)

$$\frac{\partial L}{\partial \beta} = \sum (Y-p)X = 0 \quad (10)$$

and solving equation (10) using iterative reweighted least squares, the MLE of β becomes (11)

$$\beta_{MLE} = S^{-1}X'\hat{G}\hat{z} \quad (11)$$

where $X'\hat{G}X\hat{z}$, $\hat{G} = diag(\hat{p}_i(1-\hat{p}_i))$ and $\hat{z}_i = In(\hat{p}_i) + \frac{y_i - \hat{p}_i}{\hat{p}_i(1-\hat{p}_i)}$

Hypothesis Testing for Parameters

For testing

$$H_0: \beta_i = 0$$

$$H_1: \beta_i \neq 0 \quad (12)$$

The hypothesis in (12) above is tested using the Wald statistics. The test statistic is a generalization of the function or statistic. The test statistic as given by [20] is shown in equation (13)

$$W = \left|\hat{\beta}_i - \beta_i\right|^2 / var(\hat{\beta}_i) \quad (13)$$

The Wald test major drawback is evident when the true parameter value is extremely far from the hypothesised value. Such situation results into a large standard error estimate. Generally stating, whenever the estimate $\hat{\beta}_i$ is tending towards infinity other test such as the likelihood ratio test should be used in place of Wald test.

For large n W is distributed as χ^2 distribution with 1 degree of freedom

Imbalanced Dataset and Binary Classification Model

Imbalanced datasets can be a challenge in binary classification models. This situation is usually encountered in practical applications where there is random oversampling of the dominant/ majority class in the population. In practical application such as rare disease discovery it is almost certain that random sampling from the population will result into selecting more samples from the majority/dominant class. i.e., a larger percentage of individuals without the disease will be included in the sample. A fitted binary classification model usually predicts more outcome from the majority class and fewer outcomes from the minority class because the data that was used has a skewed class distribution. Model evaluation criteria like CV model accuracy tend to become bias for a dataset with skewed class distribution. To deal with this challenge and to improve the performance of the model, a data resampling approach known as Synthetic Minority Oversampling Technique (SMOTE) can be used. The technique is specifically designed to tackle imbalanced datasets by generating synthetic samples for the minority class.

SMOTE is an oversampling technique in which synthetic samples are generated for the minority class. It helps to overcome the problem of overfitting created by random oversampling. The technique focuses on the feature space to generate new instances with the help of interpolation between the positive instances that lie together. It working procedure starts by selecting the number of oversampling observations needed, then a positive class instance is selected at random to begin iteration. Thereafter KNN (K=5) for this positive instance is obtained and finally, new observations of these K instances are chosen to interpolate new synthetic instances. More details about SMOTE can be found in [21]. In this work, the R code for SMOTE algorithm was used for resampling the training dataset.

Model Performance Metrics

In selecting the most precise machine learning algorithm for prediction a number of criteria can be used. Some of these criteria as described by [22] is defined below.

Sensitivity: the probability that a counterfeit medicine (F^+) will be correctly classified as counterfeit by the fitted model (M^+). Mathematically as shown in equation (14)

$$P(M^+/F^+) = P(M^+ \cap F^+)/P(F^+) \quad (14)$$

Ssensitivity can also be described as the percentage of counterfeited antimalarial correctly predicted by fitted model

Specificity: the probability that an original medicine (F^-) will be correctly classified as original by the fitted model (M^-). Mathematically represented in equation (15)

$$P(M^-/F^-) = P(M^- \cap F^-)/P(F^-) \quad (15)$$

Specificity can also be described as the percentage of genuine or original antimalarial correctly predicted by the fitted model.

Model Accuracy: this is the probability that a randomly selected medicine will be correctly classified by the fitted model. Mathematically, it is denoted by equation (16)

$$MA = P(F^+) \times \text{sensitivity} + P(F^-) \times \text{specificity} \quad (16)$$

The cross-validation model accuracy is used in model selection other metrics or criterion including accuracy, specificity, sensitivity will be calculated using the test data set for model performance evaluation.

Results

The results presented in this section were obtain after analysing the data using the methodology described in the last section.

The frequency distribution of SSL results of antimalarial for the six zones is presented on table 1; the results is based on the entire sample size of 4263 medicines. The estimate of the parameters of the BLR model for zones using the training data is presented on table 2. Also presented on this table are the standard error of the estimates, the Wald values, p-values are and exponent for each parameter estimates. The CV model accuracies of four BLR models (M1, M2, M3, M4) fitted using the training data and different varieties of its resampling with the SMOTE algorithm is presented on table 3. The training data includes 33% of the minority class (class of antimalarial that failed SSL test), the Resampled Training Data 1 (RTD 1) includes 40% of the minority class. Also, RTD 2 and RTD 3 includes 45% and 50% of the minority class respectively. Presented on table 4 is the model performance metrics of these BLR models using the testing data. The confusion matrix of the models M2 and M4 are presented on table 5 and 6 respectively.

Table 1: Frequency Distribution of the Standard Laboratory Results for Geographical Zones

	SSL Results			
Zones	**Fail**	**Pass**	**Total**	**% Pass**
North Central	66	253	322	21.4%
North East	121	133	490	47.6%
North West	149	288	437	34.1%
South East	189	232	431	44.9%
South-south	72	306	377	19.0%
South West	207	423	630	32.9%
Total	807	1631	2442	33.0%

Table 2: Parameter Estimates of the BLR Model for Zones

Zones	Parameter Estimator (β)	Standard Error	Wald Value	P- Value	Exp (β)
North Central	0.44	0.19	5.55	0.019	1.555
North East	-0.62	0.18	12.29	0.000	0.538
North West	-0.052	0.16	0.10	0.750	1.053
South East	-0.484	0.16	9.67	0.002	0.616
South-South	0.612	0.18	11.37	0.001	1.844
Constant	0.724	0.10	50.50	0.000	2.063

Table 3: Cross Validation BLR Model Accuracy for different Varieties of Training Data

Model	Data used to fit Model	% Of the Minority Class Sampled	CV Model Acc.%	Kappa
M1	Training Data	33%	67%	0.000
M2	RTD 1	40%	61.3	0.147
M3	RTD 2	45%	60.2	0.171
M4	RTD 3	50%	57.7	0.154

Table 4: Model Performance Metrics (Testing Data)

Data used to fit Model	Model Accuracy	Sensitivity	Specificity	Prevalence
Training Data	67%	0	1.0	33.1%
RTD 1	65.6%	0.372	0.796	33.1%
RTD 2	65.6%	0.372	0.796	33.1%
RTD 3	56.8%	0.636	0.535	33.1%

Table 5: Confusion Matrix for Model 2 (Testing Data)

Observed SSL Result			
Predicted SSL Result	**Fail**	**Pass**	
Fail	90	100	
Pass	152	390	
Overall Percentage			65.6

Table 6: Confusion Matrix for Model 4 (Testing Data)

Observed SSL Result			
Predicted SSL Result	**Fail**	**Pass**	
Fail	154	228	
Pass	88	262	
Overall Percentage			56.8

Discussion

The results presented on table 1 showed that a total of 2442 antimalarial were sampled across the six zones of the country. Specifically, 322 antimalarial were sampled from north-central zone, 490 were sampled in north-east zone, 437 sampled from the north-west zone, 431 were sampled from the south-east, zone 377 were sampled from south-south zone and 630 antimalarial were sampled from the south-west zone. The results further showed that 21.4%, 47.6% 34.1% of the sampled antimalarial failed the SSL test in the north-central, north-east and north west zones respectively. This represents the percentages of counterfeit antimalarial within the three northern zones. Likewise, 44.9%, 19% and 32,9% failed the SSL test in the south-east, south-south and south-west zones respectively. This also represents the percentages of counterfeit antimalarial within the three southern zones. Overall, 33% of the antimalarial sampled across the country failed the SSL. test, which suggest that one-third of the entire population of antimalarial within the country is counterfeited.

Parameter estimate of the BLR model for zones using south-west as the reference zone presented on table 2 showed a Wald test value of 5.55 for north-central, 12.29 for north-east, 0.10 for north-west. 9.67 for south-east and 11.67 for south-south. The p-value revealed statistical significance at 2% level for all zones except north-west. The implication of the result is that the incidence of counterfeit antimalarial in the south-west zone is statistically different from the incidence of antimalarial in all the other zones except the north-west. The odd ratio for north-central, north-east and north-west are 1.56, 0.54 and 1.06 while the odd ratio for south-east and south-south 0.62 and 1.84. and 4.33 respectively. These results indicate that antimalarial sampled from south-west is 55% and 84.4% more likely to fail SSL test than those sampled in the north-central and south-south respectively. In other words, there is a lesser incidence of counterfeit antimalarial in the north central and south-south zone than in the south-west zone. Also, antimalarial sampled

from south-west is 46.2% and 38.4% less likely to fail SSL test than those sampled in the north-east and south-east respectively. In other words, there is a higher incidence of counterfeit antimalarial in the north-east and south-east zones than in the south-west zone.

The results presented on table 3 showed that the model fitted with the training data (M1) has the largest CV model accuracy of 67% i.e., 67% of antimalarial were correctly classified by M1. Other models fitted with RTD 1 (M2), RTD2 (M3) and RTD 3 (M4) have CV model accuracies to be 61.3%, 60.2% and 57.7% respectively. Although M1 has the largest CV model accuracy, it cannot however be selected has the optimal model because its confusion matrix showed that M1 only correctly classified all antimalarial within the majority class (the class that passed SSL test) i.e., M1 did not correctly classify any counterfeited antimalarial. Therefore, M1 cannot be selected as the optimal model since it is biased towards the minority class and over resampling of this class is necessary to obtain a more suitable model. Amongst model fitted with resampled data, M2 has a slightly larger CV model accuracy than M3 and M4.

The performance of these four models to the testing data presented on table 4 showed that model accuracy of M1 is 67% while that of M2, M3 and M4 are 65.6%, 65.6% and 56.8% respectively. The sensitivity and specificity of M1 is 0 and 1 respectively. Ssensitivity is the percentage of counterfeit antimalarial correctly predicted by M1 while specificity is the percentage of genuine or original antimalarial correctly predicted by the optimal model. The result showed that none of the 242 counterfeited antimalarial in the testing dataset were correctly predicted by M1 whereas all of the 490 genuine antimalarial were correctly predicted by the M1. The sensitivity and the specificity of M2 are 0.372 and 0.796 respectively. The result presented on table 5 showed that that 90 of the 242 counterfeited antimalarial in the testing dataset were correctly predicted by M2 representing only 37.2% whereas 390 of the 490 original or genuine antimalarial in the dataset were correctly predicted by M2 representing 79.6%. These sensitivity and specificity values are also the same for M3 and the above interpretation for M2 holds. It is to be noted that oversampling of the minority class from 33% as in M1 to 40% as in M2 has increased the sensitivity from 0% to 37.2%. M2 therefore has a higher capability of detecting counterfeited antimalarial than M1.

The sensitivity and the specificity of M4 are 0.636 and 0.535 respectively. The result presented on table 6 showed that that 154 of the 242 counterfeited antimalarial in the testing dataset were correctly predicted by M4. This represents 63.6% of counterfeited antimalarial in the dataset. Likewise, 262 of the 490 original or genuine antimalarial in the dataset were correctly predicted by M4. This represents 53.5% of genuine antimalarial in the dataset. It is to be noted that oversampling of the minority class from 40% as in M2 to 50% as in M4 has drastically increased the sensitivity from 37.2% to 63.6%. M4 therefore has a higher capability of detecting counterfeited antimalarial than M2. This has however come with a cost to the specificity and the overall model accuracy because specificity has also reduced from 79.6% in M2 to 53.5% in M4 and overall accuracy from 65.6% in M2 to 56.8% in M4.

Overall, zones do not seem to be a good classifier or predictor of counterfeited antimalarial in Nigeria because the best performing models are only able to correctly classify about 66% of antimalarial leaving 44% as incorrectly predicted.

Conclusions

This study assessed the prevalence of counterfeited antimalarial within the six geographical zones of Nigeria using data generated from a nationwide survey on counterfeited medicine by NAFDAC. Randomly selected antimalarial from each zone were tested for originality in a Standard Scientific Laboratory. The Binary logistic regression model which is a machine learning classification model was fitted to training data and three varieties of its resampling. These three varieties were generated using the synthetic minority oversampling technique. The four models namely M1, M2, M3 and M4 were fitted with data containing 33%, 40%, 45% and 50% of the minority class respectively. The 10-fold Cross Validation (CV) was also performed on the training data and each of its resampling varieties. The performance of the four fitted models were thereafter assessed with metrics like sensitivity, specificity and model accuracy. The result revealed that M2 and M3 performed better in terms of model accuracy and specificity while M4 was better in terms of model sensitivity. The work further revealed that there is a higher incidence of counterfeit antimalarial in the north-east and south-east zones than in the other three zones of Nigeria. The north-east zone could have been more targeted by syndicate of counterfeit medicine because of the unrest in the zone due to insurgency for the last 15years. The Onitsha main market which is the largest market in Africa by geographical size and volume of goods is within the southeast zone. This market is very strategic in the distribution of drugs to other parts of the country and it has been said that if counterfeit product can be checked in Anambra State, a large part of the menace in the country would have been solved. The results of this study can therefore assist policymakers in making data driven decisions on counterfeited antimalarial in Nigeria.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper."

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