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Modeling malaria control intervention effect in KwaZulu-Natal, South Africa using intervention time series analysis

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Abstract The change of the malaria control intervention policy in South Africa (SA), re-introduction of dichlorodiphenyltrichloroethane (DDT), may be responsible for the low and sustained malaria transmission in KwaZulu-Natal (KZN). We evaluated the effect of the re-introduction of DDT on malaria in KZN and suggested practical ways the province can strengthen her already existing malaria control and elimination efforts, to achieve zero malaria transmission. We obtained confirmed monthly malaria cases in KZN from the malaria control program of KZN from 1998 to 2014. The seasonal autoregressive integrated moving average (SARIMA) intervention time series analysis (ITSA) was employed to model the effect of the re-introduction of DDT on confirmed monthly malaria cases. The result is an abrupt and permanent decline of monthly malaria cases ($w_0 = -1174.781$, p-value = 0.003) following the implementation of the intervention policy. The sustained low malaria cases observed over a long period suggests that the continued usage of DDT did not result in insecticide resistance as earlier anticipated. It may be due to exophagic malaria vectors, which renders the indoor residual spraying not totally effective. Therefore, the feasibility of reducing malaria transmission to zero in KZN requires other reliable and complementary intervention resources to optimize the existing ones.

Introduction

South Africa (SA)'s malaria vector control (i.e., intervention) depends mainly on indoor residual spraying with dichlorodiphenyltrichloroethane (DDT). As an implication, SA in general and KwaZulu-Natal (KZN) in particular have made significant progress over the past two decades in reducing malaria disease caused by *Plasmodium falciparum* [1,2]. This decline can be associated with the change of SA's malaria vector control policy during the peak of the 1999/2000 malaria epidemic. In March 2000, DDT was re-introduced for malaria vector control purposes after it was discontinued in 1995. The re-introduction and continued use of DDT have been possible because the national government, with the help from international scientists and an independent advocacy group successfully obtained an exemption in the Stockholm Convention on Persistent Organic Pollutants in 2000 [1]. After DDT was introduced in March 2000, an abrupt decline in malaria cases was observed in the time series data [3]. While the level of malaria control achieved in KZN is encouraging, local transmission has

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not reached zero [1,2], thus, it remains a cause for concern for SA as she targets malaria elimination in 2020 [2].

The impact of the re-introduction of DDT (the known intervention) in KZN is assumed to be associated with the notable alteration of the malaria time series or change of the mean function [3] and can be evaluated employing an intervention time series analysis (ITSA) [4,5]. The ITSA is a thorough and reliable analytical method that allows the effect of an intervention to be separated from the general trends and serial dependencies in time, thereby allowing sound statistical inference to be made if the intervention had an effect on the time series [4,5]. This method gives analysts the opportunity to draw inferences from the impact assessment and confirms the substantive notion of a particular area or region. In other words, the ITSA model can be the best form of impact assessment from a statistical point of view as long as the inference(s) and conclusion(s) drawn from the analysis is/are reconciled with the prevailing theory in a substantive sense [4]. Substantial ITSA studies applied the univariate approach due to its simplistic application in modeling and data availability [6–10]. Similarly, the impact of the re-introduction of DDT in KZN can be reliably evaluated employing the same approach.

This paper thus attempts to determine if the long-term use of DDT significantly lead to the decline and ultimately will lead to zero malaria transmission in KZN. The outcome of this study will serve as a validation of the substantive significance of DDT on malaria in KZN. This is vital to the province's malaria control and elimination efforts because it will bring to light the necessity of identifying other practical ways that can be used to upscale the existing malaria vector control strategies to achieve zero malaria transmission. Thus, this study also seeks to suggest other reliable and complementary intervention resources that can support and optimize the already existing interventions. It is for these reasons that the historical series of malarial cases in KZN will be utilized as the dependent series, in the univariate seasonal autoregressive integrated moving average (SARIMA) model with known intervention, and its characteristics will allow the behavior of malaria over time, to be evaluated.

Materials and methods

Study area

The three district municipalities (uMkhanyakude, uThungulu, and Zululand) in KZN province endemic to malaria were included in this study (Fig. 1). uMkhanyakude is situated in the northern region of KZN province with a population of 625,846 [11]. uThungulu and Zululand district municipalities are located in the north-eastern part of KZN province with a population of 907,519 and 803,575 respectively [11]. The study areas are bordered by Swaziland and Mozambique to the north and the Indian Ocean stretching from the east down to the southeast. The province is characterized by the sub-tropical climate with most of the malaria cases occurring during the rainy months (October to May), with a seasonal peak usually in January and March [2,12].

Data source

Monthly aggregates of clinically confirmed malaria cases from January 1998 to December 2014 were collected from the malaria control program of KZN, SA. A malaria case is a person whose blood smear tested positive to *Plasmodium* after undergoing a rapid diagnostic test or slide microscopy at a health facility [13]. Since 1956, it became a legal requirement to notify malaria cases to the relevant health authorities in SA [14]. Confirmed malaria cases at health facilities are reported to the relevant district health office which is subsequently reported to the provincial malaria control program. At the provincial malaria control program, the malaria control worker collects and inputs information relating to the malaria case into the malaria information system. The information includes patient's personal details, the health facility the case was reported, symptoms, malaria test results, diagnosis and type of treatment administered [2,15].

Analytical method

We employed the Box and Tiao approach of the ITSA [16] to examine the effect of the malaria intervention. It involved a two-step analytical process. The first step is the identification of the most suitable SARIMA model, referred to as the noise component of the model, using the dataset not impacted by the intervention or before the intervention. This part of the ITSA is bounded by Box and Jenkin's SARIMA model approach [17], and it involves the following steps: model identification, parameter estimation, and diagnostic checking. Exhaustive presentations of these procedures are found elsewhere [4,17,18]. The second step involves re-estimating the identified model using the full dataset to test the effects of the intervention on the behavior of the time series, and it is known as the intervention component. Hence, by comparing the level of pre-intervention and post-intervention time series, the statistical significance of the intervention was evaluated.

The ITSA model is written as [16]:

$$Y_t = f(I_t) + N_t \tag{1}$$

Where Y_t denotes the dependent variable for a certain time or is an observed time-series, the function $f(I_t)$ denotes a ''function of the variable I_t'', the intervention component (also referred to a transfer function), N_t denotes the noise component determined by an univariate SARIMA (p,d,q) (P,D,Q) structure and t denotes the discrete time.

The impact of an intervention on the time series can be either abrupt or gradual in onset and either permanent or temporary in duration. Therefore, the shape of the time series after the onset of an intervention determines which transfer function (i.e., zero order transfer function, first order transfer function or pulse function) will be used to model the impact [4]. Our time series data shows that the response of the malaria cases after the onset of the known intervention (i.e. re-introduction of DDT) had an abrupt and permanent shift in the process. We, therefore, used a ''zero order transfer function'' to determine the effect of the re-introduction of DDT in KZN.

The zero order transfer function is written as [4]:

$$f(I_t) = W_0 I_t \tag{2}$$

Where w_0 denotes the parameter estimate of a transfer function. The variable I_t is defined as a step variable or step variable such that,

$I_t = 0$ before the intervention

and $I_t = 1$ at and after the intervention.

Therefore the impact assessment model is:

$$Y_t = w_0 I_t + N_t \tag{3}$$

From our time series, $I_t^{03/2000}$

$$= \begin{cases} 0 \text{ if } t < 03/2000 \text{ (before the intervention)} \\ 1 \text{ if } t \geq 03/2000 \text{ (at and after the intervention)} \end{cases}$$

Software

All the modeling and analysis in this study were performed using the R statistical software version 3.2.3. The map showing the study area was developed using the ArcGIS 10.2 software (ESRI, Redlands, CA, USA).

Results

Exploratory data analysis

The time series of confirmed monthly malaria cases from January 1998 to December 2014 in KZN is shown in Fig. 2. Before the re-introduction of DDT, the time series shows markedly increase in malaria cases. The re-introduction of DDT into the SA malaria control program in March 2000, coincided with the beginning of the abrupt decline of malaria cases in KZN which continued until June 2001. Afterward, relatively low and sustained cases were recorded with a noticeable spike between December 2003 to November 2004. The quick decline in malaria cases after November 2004 and sustained low malaria cases onwards can be attributed to the continuous application of the intervention. Overall, this is a good example of a time series that the impact of the known intervention is abrupt in onset and permanent in duration. Thus, an empirical assessment of the