Letter to the Editor

(for publication)

CEREBRAL MALARIA ADMISSIONS IN PAPUA NEW GUINEA MAY SHOW INTER-ANNUAL CYCLICITY: AN EXAMPLE OF ≈1.5-YEAR CYCLE FOR MALARIA INCIDENCE IN BURUNDI

Borislav D Dimitrov MD MSc PhD [1,#] and Penka A Atanassova MD PhD [2]

[1#]BORDANI, Alzano Lombardo, Bergamo, Italy; and

[2] Department of Neurology, Medical University, Plovdiv, Bulgaria

Running head: Inter-annual cyclicity of malaria in Papua New Guinea and Burundi

Precise forecasting of incidence trends and better allocation of resources are invaluable for national health systems worldwide. Best available descriptions of malaria incidence and mortality dynamics are important to better plan and evaluate the implementation of programs to monitor (e.g., remote sensing) and control the disease, especially in endemic zones. This was stressed recently by Cibulskis an collaborators [1] in the view of completeness of monthly reporting for cerebral malaria admissions in Papua New Guinea (latitude 6°S) in the interval 1987-1996. Regardless of the rate of its completeness, the dynamics of admissions was preserved over the years, however, neither raw data nor results on further analyses about eventual inter-annual cyclic components (periods T>1 year) were provided despite obvious graphical patterns for such chronome (time structure). Interestingly, a recent analysis by Gomez-Elipe and collaborators [2] on monthly malaria notifications in the province of Karuzi, Burundi, at almost the same latitude >3°S (1997-2001), has shown neither trend not periodic oscillations beyond a 6-month (0.5-year) period. Owing to environmental interactions, it is not unlikely that seasonal variations in malaria (e.g. 12-month cycle) may be damped by frequent rainfall or irrigation practices [3] but, irrespectively, inter-annual (infrannual) cyclicity might persist and, if searched for, eventually revealed.

Based on the graphical representation of both data sets (Papua New Guinea and Burundi) which indicate an eventual existence of inter-annual variations, and because both are located at almost similar latitude zones (3-6°S), we have aimed at analyzing the data from Burundi and search for such periodic oscillations (periods T>1 year). Although we are not able currently to analyze the data from the paper by Cibulskis et al [2], we have hypothesized that similar inter-annual cyclicity may also exist in the chronome of cerebral malaria admissions in Papua New Guinea (irrespectively of the reporting modes and their completeness). Possible temporal associations of such inter-annual cyclic components in malaria incidence with environmental factors exhibiting alike cyclicity (solar activity, geomagnetic storms, etc.) might also exist.

For the purpose of this report, the incidence rates of malaria per 100 inhabitants in the Province of Karuzi, Burundi during the interval 1997-2001 (Table 2 in Gomez-Elipe *et al* [2]) were considered. The incidence consisted of all new cases defined as *"case of malaria is a patient seeking medical attention with fever over 38°C and no signs of acute respiratory infection, urinary infection, otitis, meningitis, measles or abscesses."* for monthly notification purposes. The original datasets were present as observed and estimated incidence rates. Different statistical methods for time-series analyses and modeling were used including descriptive statistics, linear and non-linear regressions over time and, specifically, a periodogram regression analysis (PRA) and statistical tests with 95% confidence limits. PRA was described and successfully used in studying periodicity in other infectious diseases previously [4-5]. In particular, the correlation-regression function ***F(t)*** of periodic mode for monthly incidence values is presented bellow:

$$F(t) = a_0 + A\cos\frac{2\pi t}{T} + B\sin\frac{2\pi t}{T} \qquad /1.0/$$

where a_0 is the mean value of the frequency f in the sample, A and B are coefficients of the regression for the actual frequency values $f(t)$ in the presence of a fixed period T, t is the current moment of time (a serial number of the month: 0, 1, 2, 3, ..., n-1), and n is the total number of monthly values in the series of data. As a result, a spectrum of coefficients of correlation R between $f(t)$ and $F(t)$ have been calculated. When the chosen period T is similar to some cycle existing in the actual values, then R is higher (peak) and statistically significant (**Figure, Panel B**). The spectrum of R (periodogram) was obtained for different cycles by variation of T with a step δT (e.g., 0.5 months) from some preliminary chosen minimal value T_0 (if the time-series discretization is 1 month, T_0 = 2 months).

By using PRA, we discovered a multicomponent inter-annual cyclic pattern with periods >12 months (T=17.5-18.0, 27.5 and 65.0-65.5 months, all at $p<0.05$, not shown) in the malaria incidence dynamics in Burundi. To control for the influence of eventually existing linear or non-linear (cyclic) tendencies on above inter-annual cyclicity in the chronome (time structure), the original (observed) time series was transformed by removing the linear trend (detrended). It may be clearly seen that the when we removed the trend, this has not changed in any way the temporal dynamics (**Figure, Panel A**) including both the epidemic peak and cyclic variations (see the thick curve). Notably, the most strong cyclic pattern at $p<0.002$ in the periodogram of the detrended malaria rates remained only that with a period of ≈1.5 years *(period T=17.5-18.0 months, R=0.51, z=5.3)* (**Figure, Panel B**). It is possible that likely inter-annual cyclic patterns might exist also in the cerebral malaria admissions in Papua New Guinea and, if confirmed, these may be found very useful in epidemic forecasting and programs implementation. For instance, such similarity in the cyclic variations of sexually-transmitted diseases between different countries (e.g., Slovakia and UK), those possibly being one of the underlying causes for incidence resurgence [6], was also explored successfully earlier by above periodogram regression analysis [5,6].

Last but not least, such inter-annual cyclicity in malaria incidence rates in endemic areas, of 1.5 years (trans-year), may correspond to and be associated with known but rarely studied environmental cyclicity of 1.3-1.5 years in heliophysical activity (e.g., solar wind, solar magnetic activity, etc.). The solar (sunspot) cycle may consist of several impulses with periods about 0.5-2.0 years; notably, a high-frequency component of 1.5-2.5 years (quasi-biennial cycle) exists in the solar magnetic cycle [7] as seen during the 3-fold polar magnetic field reversals (i.e., separations of zones of alternated polarity of the magnetic field). The expressions of above magnetic activity and its influences on the disease incidence (and why not, on the transmission rate) might be considered very similar across different countries and, possibly, across many decades and, why not, centuries (interestingly, in this sense, a far-reaching idea by Dr Merritt, called “A valuable theory”, about eventual associations between “chills and fever” or other forms of “malarial disease”, with “marked

influence upon the nervous system", and the "spots on the sun" had been picked-up by *The New York Times* still in April 1882!).

Notably, such univariate *(cyclicity)* and eventual bi-variate *(lagged correlation)* temporal relationships with cyclic environmental factors might contribute not only to better forecasting of malaria incidence trends. These associations might also foster the research on the role of global and very ancient, but not directly or easily treatable physical ecological factors in the etiology, progression and transmission of malaria well as in the environmental epidemiology of other tropical diseases.

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Authors' addresses:

Borislav D Dimitrov, Via Lombardia 12, Alzano Lombardo (BG), 24022, Italy.

Penka A Atanassova Department of Neurology, Medical University, 15A V Aprilov Blvd, Plovdiv, 4000, Bulgaria

Reprint requests:

Borislav D Dimitrov, Via Lombardia 12, Alzano Lombardo (BG), 24022, Italy (e-mail: bdd11@yahoo.com)

Legend to Figure

Figure **Cyclical patterns in the dynamics of malaria incidence in the Province of Karuzi, Burundi (1997-2001)**

Panel A: Monthly incidence malaria notifications. The chart illustrates the temporal dynamics of observed *(dots)*, expected *(thin line)* and detrended observed *(thick line)* incidence rate per 100 inhabitants. *The data on observed and expected incidence rates were taken from Table 2 by Gomez-Elipe et al*[2] .

Panel B: Periodogram regression analysis of the detrended observed incidence rate per 100 inhabitants. The resulting spectrum of the coefficients of correlation (R, periodogram) illustrates an inter-annual cycle of about 1.5 years as denoted by the peak on the periodogram (period T=18 months, *vertical arrow*). The horizontal lines *(dashed)* indicate the theoretical value of R at two selected levels of significance ($p=0.05$, $p<0.002$).

Summary

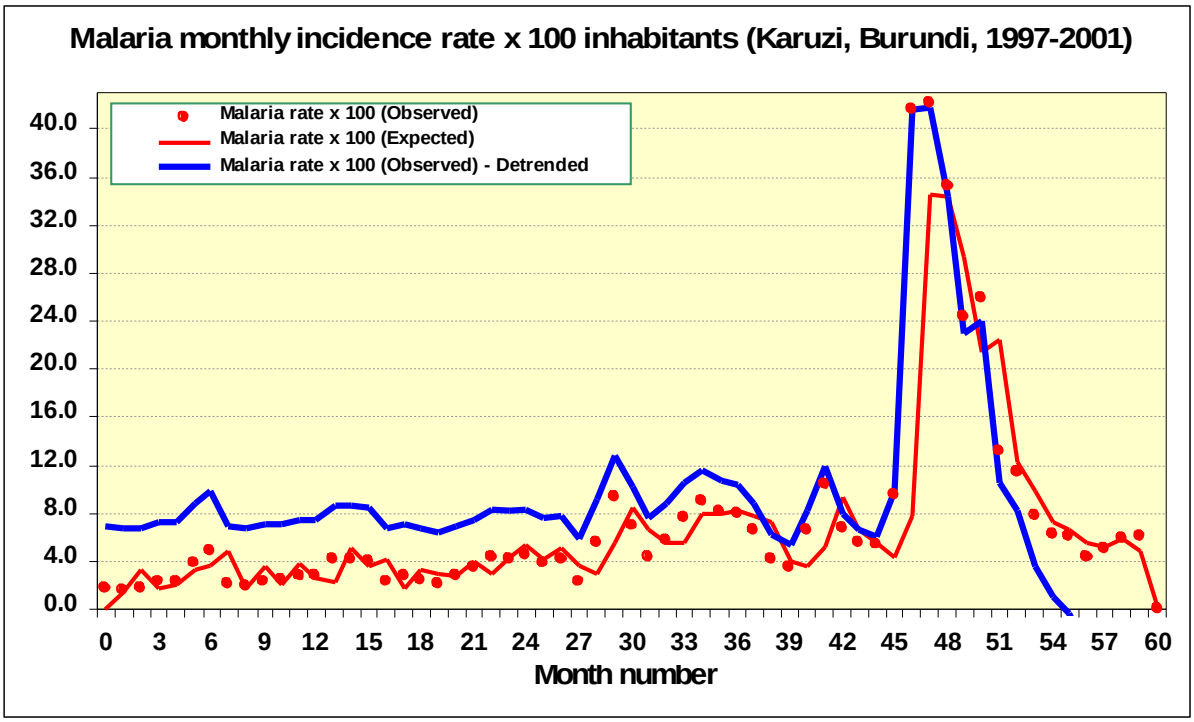
Best available descriptions of malaria incidence and mortality dynamics are important to better plan and evaluate the implementation of programs to monitor (e.g., remote sensing) and control the disease, especially in endemic zones. This was stressed recently by Cibulskis et al (2007) in the view of completeness of monthly reporting for cerebral malaria admissions in Papua New Guinea (latitude 6°S, 1987-1996). Notably, regardless of the rate of its completeness, the temporal dynamics of admissions was preserved over the years, however, neither raw data nor results on further analyses about eventual inter-annual cyclic components (periods T>1 year) were provided despite obvious graphical patterns for such a specific time structure (chronome). Interestingly, in a recent analysis by Gomez-Elipe et al (2007) on monthly malaria notifications in Burundi, at almost the same latitude (province of Karuzi, >3°S, 1997-2001), the data have shown neither trend not periodic oscillations beyond a 6-month (0.5-year) period. Since the graphical representation of both data sets have indicated an eventual existence of inter-annual variations, and because both are located at the same latitude zone, we have further analyzed the data from Burundi for such periodic oscillations. By using a periodogram regression analysis, we discovered a multicomponent cyclic chronome with periods above 12 months (T=17.5-18.0, 27.5 and 65.0-65.5 months, all at $p<0.05$). Notably, the most strong cyclic pattern at $p<0.002$ in the periodogram of the detrended malaria rates in Burundi remained only that with a peak at ≈1.5 years (period T=17.5-18.0 months, R=0.51, z=5.3). It is possible that likely inter-annual cyclic patterns might exist also in the time structure for cerebral malaria admissions in Papua New Guinea and, if confirmed, these may be found very useful in epidemic forecasting and programs implementation. We explored these cyclic variations and also discussed possible associations with environmental factors exhibiting alike cyclicity.

Keywords: *Malaria, cerebral, incidence, cyclicity, periodogram regression analysis*

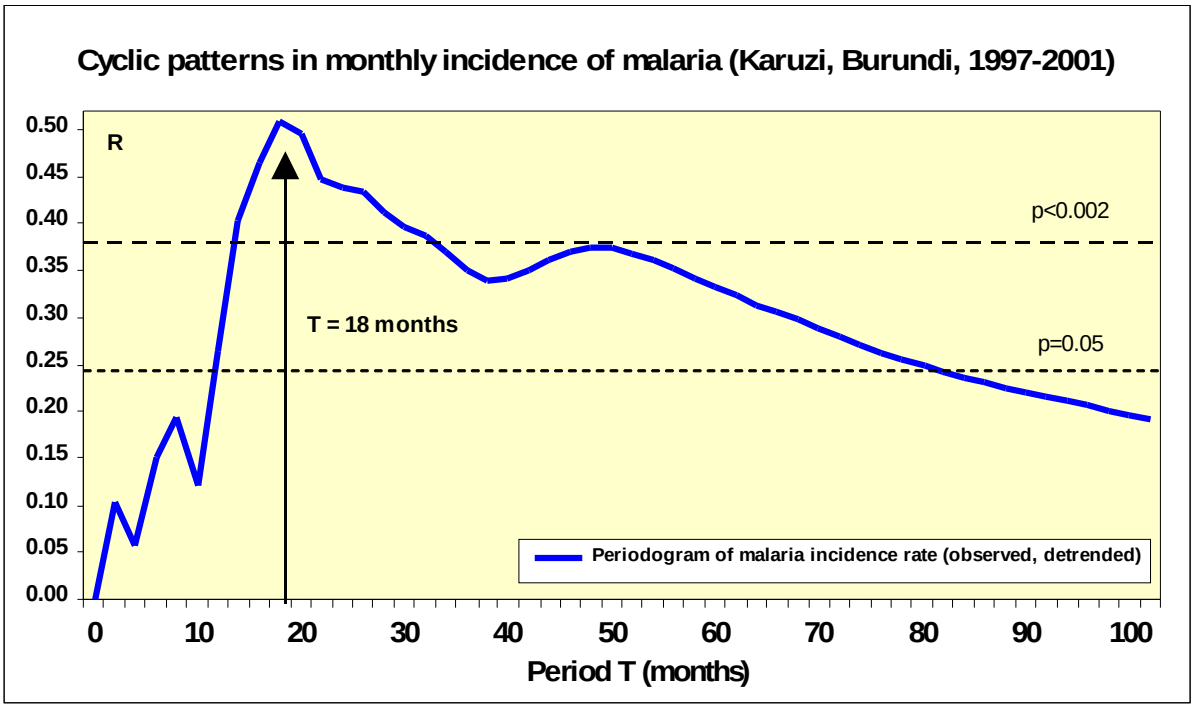
#*Corresponding author:*

Dr Borislav D Dimitrov, MD, MSc, PhD
BORDANI Via Lombardia 12
Alzano Lombardo, Bergamo, 24020, Italy
tel/fax: +39035510728
e-mail: bdd11@yahoo.com

Panel A



Panel B



Figure