Influenza in the tropics: The role of humidity

Liat Vaisenberg[1]
liat.ronen@gmail.com

Andrew Noymer[2]
noymer@uci.edu

(1) Program in Public Health, University of California, Irvine

(2) Department of Population Health and Disease Prevention, University of California, Irvine
Department of Sociology, University of California, Irvine
Health and Global Change project, IIASA, Laxenburg, Austria

Paper submitted to PAA 2011, Washington DC

Abstract

To test hypotheses of the seasonality of influenza, we analyze the pairwise comovements of the incidence of influenza and malaria, and of influenza and chickenpox, in the tropical country of Burundi. We use the Goodman-Grunfeld nonparametric test for comovement between two time series, correcting for serial correlation. We find a significant comovement between influenza and malaria, suggesting that humidity, an important factor in the transmission of malaria, also plays a role in influenza transmission, at least in the tropics. No comovement was found between influenza and chickenpox, implying that crowding effects are not a significant factor in the seasonality of influenza in the tropics. We show that an indirect method may provide information that would otherwise elude direct analysis. Our data suggest that either the driving factors of cyclicality, or modes of influenza transmission, or both, may work differently in the tropics than in temperate regions.

1 Introduction

Influenza A virus causes worldwide epidemics annually, resulting in considerable morbidity and mortality. For example, in the United States in a typical influenza (flu) season, more than 200,000 people are hospitalized from flu complications, and approximately 36,000 people die from flu-related causes [1, 2]. The elderly, young children and those with certain health conditions are at a high risk for serious flu complications. Influenza is seasonal: in temperate climates, the disease exhibits a marked increase during the winter, typically between December and April in the northern hemisphere, and between June and September in the southern hemisphere [3]. The reasons for the seasonality of the flu are not well understood. Some researchers suggest that climate plays a major role, by affecting viral survival or transmission efficiency [4].

Seasons may also affect host susceptibility to infection in temperate regions, because winter reduction in sunlight exposure lowers production of vitamin D, weakening the immune system [5]. Climate may also cause indirect effects such as behavioral changes in human crowding, where, for example, people remain in closed and confined quarters during the winter [6]. Tropical and sub-tropical regions also display seasonal effects, although less pronounced [7]. This suggests a complex mechanism underlying seasonal effects, and seasonal consistency is still poorly understood. For simplicity, we refer hereinafter to cyclical incidence as seasonality, even in the equatorial context where the temperate seasonality of winter, spring, summer, and fall, does not apply.

Understanding influenza patterns is crucial for vaccination timing and correct vaccine strain identification. Ideally, control strategies will be adjusted according to individual regions using their own seasonal characteristics. Currently, only two vaccine compositions, corresponding to the northern and southern hemispheres, are recommended annually by the World Health Organization [8]. The influenza A viral genome drifts gradually over time

and new strains spread globally [9]. More dramatic strain changes are known as antigenic shifts, and precipitate pandemics [10]. Understanding the patterns of influenza in equatorial regions can aid in optimizing strain collection and vaccination timing in the tropical regions, and help to shed light on the basic biology of influenza virus transmission.

A variety of social, demographic and environmental factors have been linked to influenza transmission. Children are thought to play a major role in the dissemination of influenza in households and schools [11]. Cold temperatures and low relative humidity are thought to be favorable for the spread of the virus [4]. Confinement to closed spaces especially favors viral transmission [6]. The substantial overlap between these factors and the seasons per se complicates causal assignment. The tropics, which have influenza, but different seasonal patterns, provide a useful natural experiment in influenza cyclicality. In tropical regions, however, there has been less influenza research [12]. Heat and high humidity have been suggested to enhance virus survival and, therefore, to activate seasonal patterns [13]. Temporal patterns in tropical and sub-tropical regions have been linked with both environmental and population determinants to explain the wave of influenza in Brazil [14].

We investigate flu seasonality by comparison to the seasonal patterns of two other diseases, chickenpox and malaria. Chickenpox is a highly contagious disease caused by primary infection of varicella zoster virus. It is estimated that, in the absence of vaccine, the lifetime risk for varicella infection is over 95%, with most cases occurring during the first 15 years of life [15]. Contact rates are the driving factor in chickenpox epidemics [16, 17]. There is, therefore, a strong linkage to the school calendar. A pre-vaccination study in Canada and the United Kingdom demonstrated case increases during the school year (September to June) and a sharp decline during the summer (June to September) [18]. The disease spreads primarily by direct contact and airborne transmission; important

exposure hubs are classmates and siblings [19].

Chickenpox in the tropics is less well-studied than in temperate regions. The classic view is one of lower transmission rates, and therefore higher median of age infection [20, 21]. More recent data from urban India suggest a pattern that resembles industrialized countries, viz., high seroprevalence of varicella antibodies by adulthood, while rural areas have lower rates of chickenpox transmission, evidenced by lower sera antibody prevalences [22]. Likewise, differences were found in transmission patterns between the tropical and temperate zones of Australia [23]. On the other hand, in a sample of refugees from several tropical countries, reasonably high serum antibody prevalence was found [24]. Similarly, steep increases by age in seroprevalence of varicella zoster antibodies were found in rural Bolivia, suggesting high transmission among children and teenagers [25]. The last half-century has witnessed urbanization and increases in population density in tropical countries. This suggests that the more recent findings, of convergence in the epidemiology of chickenpox between temperate and tropical settings, are more an updating than an invalidation of the classical view of low transmission in the tropics.

Malaria is one of the most severe public health problems in sub-Saharan Africa, and its seasonality has been studied extensively to say the least. Humidity — specifically, rainfall — is well-known to be associated with malaria infection rates [26]. Rainfall and, to some extent, temperature, are important determinants of the intensity of the entomologic inoculation rate during the peak of the transmission season [27]. The causal mechanism is the development of mosquito larvae in water [28]. Peak malaria transmission thus lags peak rainfall by at least mosquito larval and pupal development times, and parasite development times within the vector. The variability (as opposed to amount) of rainfall is also important to malaria transmission in Burundi [29].

We use an indirect approach to examine the cyclical behavior of influenza in Burundi,

by comparing influenza incidence patterns to those of malaria and chickenpox. Extrapolating from the cyclicality of the comparison diseases, we test hypotheses about whether humidity or crowding are better predictors of influenza incidence. Considering our data as a time series, we use a nonparametric test of influenza incidence co-movement with chickenpox and malaria. Since malaria is so well established as a humidity-related disease, comovement between malaria and influenza would be an indication by proxy that humidity (or dryness) plays a role in influenza transmission. On the other hand, if there is also strong comovement between influenza and chickenpox, we can point to increased person-to-person contact (e.g., from the start of the school year) as playing a role in influenza. Thus we exploit two dyadic disease relationships (influenza-malaria and influenza-chickenpox) at the population level to test hypotheses about shared epidemiologic mechanisms among the three diseases.

2 Materials and Methods

2.1 Data

Burundi is a small (27,834 km^2), densely populated country in East Africa with an estimated population of 8.7 million (as of 2008) and an estimated infant mortality rate of 60 per 1,000 live births. During the time period of our data (1981–1987), the national population grew from 4.17 to 5.07 million, a growth rate of almost 3% per year [30]. This is a large growth rate, implying a population doubling time of about 23 years. Relevant for the present study, the high growth rate also makes for a young-skewed population age structure, and thus a steady stream of chickenpox-susceptible children.

Burundi has an equatorial climate with the average annual temperature between 17° to 23°C, depending on province, which is somewhat lower than other tropical countries

since the average altitude is about 1,700m. At the provincial level, annual low temperatures range from 5–12°C, and annual high temperatures range from 26–35°C. The average annual rainfall is approximately 150 cm with two wet seasons (February to May and September to November), and two dry seasons (June to August and December to January). The June–August period is the driest, with many weather stations typically reporting no measured precipitation during one or all of these months [31].

Monthly incidence data for 28 diseases, including influenza, malaria, and chickenpox, were available from reports submitted to the Ministry of Health by health centers. Cases were coded as malaria (ICD9 084) or as chickenpox (ICD9 052) or as influenza (ICD9 487). Our data are on case counts, not individual cases, and therefore detail on laboratory confirmation, etc., is not available. This surveillance data set was provided to the authors by Robert Chen of the CDC, Atlanta, and is further described in the literature [32]. At the time of the data collection, no vaccination programs against any of the three diseases were being administered. We use data spanning 81 months between 1981 and 1987. We are unaware of any available directly-measured humidity data during this time period, and thus we employ the malaria incidence data as an effective proxy.

2.2 Data analysis

We use the Goodman-Grunfeld nonparametric test of comovement between two time series [33]. This test is based on a chi-squared analysis of signs of differences of each time series, cross-classified in a 2×2 table. Thus, we analyze if cases of malaria and influenza (for example) both increase, or both decrease, or move in either permutation of opposite directions, on a month-to-month basis. Under the null hypothesis of no comovement between the two data series, the expected frequencies of the four cells of the table would be equal. Moreover, the Goodman-Grunfeld test corrects for serial correlation.

A sketch of the test follows; the particulars are given in the cited works [33, 34]. Take two time series $X = \{X_0, X_1, \ldots, X_n\}$ and $Y = \{Y_0, Y_1, \ldots, Y_n\}$, with subscripts for time periods. Create dummy (indicator) variables, $U = \{U_0, U_1, \ldots, U_{n-1}\}$ and $V = \{V_0, V_1, \ldots, V_{n-1}\}$ respectively, coded $\{0, 1\}$, to indicate period-to-period increase. That is, $U_i = 1$ if $X_{i+1} - X_i > 0$, and similarly for V_i and the Y series. Then cross-classify U and V in a 2×2 table, the cell counts of which are labeled (left to right) a, b across the top row and c, d across the bottom row; the counts of comovements are a and d and the countermovements are b and c (confer table 2 for the layout). The Goodman-Grunfeld test statistic is:

$$\frac{a - A}{\sqrt{n[(a+b)(a+c)(b+d)(c+d)/n^4 + 2ef]}} \sim N(0,1), \text{where:}$$

$$e = \sum_{i=0}^{n'-1} U_i U_{i+1}/n' - [(a+b)/n]^2, \text{ and } f = \sum_{i=0}^{n'-1} V_i V_{i+1}/n' - [(a+c)/n]^2,$$

and where $n = a + b + c + d$, $A = (a + b)(a + c)/n$, and $n' = n - 1$ is the number of sequential pairwise comparisons of U and V. The term in ef is the correction for serial correlation. The test statistic is normally distributed because of the equivalence between a normal and a χ^2 distribution with one degree of freedom. Although not shown in the above formula, we use the 'continuity correction' [35], as Goodman and Grunfeld advise. The Goodman-Grunfeld test is more conservative (i.e., harder to reject the null hypothesis of no comovement) than a naïve χ^2 analysis of the comovements. We use two-sided tests throughout.

To supplement the comovement analysis, we present elasticity plots: monthly cases of one disease against another, on log-log scale. The slope of this graph gives the elasticity, i.e., the percent change in the number of cases of one disease as a factor of the percent change in number of cases of the other disease [36, p. 227]. A measure of goodness of

Table 1: Summary of average and total cases of influenza, chickenpox and malaria in Burundi, in the study period, beginning January 1981

	Influenza		Chickenpox		Malaria	
	mean	SD	mean	SD	mean	SD
January	7924.2	1779.0	1404.0	205.9	14527.3	3626.5
February	8363.0	1486.9	1226.0	403.1	16042.3	2165.7
March	7966.7	1525.5	1257.0	409.6	14743.3	3545.0
April	8463.3	2480.9	1059.3	409.5	16021.9	4890.8
May	10383.9	2313.9	857.3	397.9	18921.7	3580.8
June	11936.6	4469.7	895.6	252.3	23278.6	7319.9
July	8944.6	1809.1	1083.9	323.7	20269.9	4714.1
August	6927.1	1133.5	1264.0	387.5	16852.1	3757.7
September	5897.7	1153.6	1177.7	331.2	15721.6	4245.2
October	6371.5	929.6	1323.9	368.0	15883.7	3937.9
November	9898.5	4387.5	1507.3	401.2	16294.9	5795.4
December	11158.3	6826.1	1750.8	296.9	17149.8	5034.4
Total cases	694,295		100,492		1,408,272	

fit of the elasticity plot provides an alternate way to measure the co-variation of the two data series; we use the R^2 of the regression line. A significant Goodman-Grunfeld p-value indicates comovement *or* antimovement, because we use two-sided tests. The elasticity plot allows visualization of whether high numbers of cases of one disease are associated with high or low numbers of cases of the other disease.

Both of these approaches (the Goodman-Grunfeld test and the fit of the log-log plot) are scale-invariant (being based on signs of differences and on percentage changes, respectively). The scale-invariance of the log-log plot has been exploited in epidemiology before [37, 38]. These methods are ideally suited to data sets, such as ours from Burundi, where there may be reporting anomalies. In other words, these methods are robust to both month-to-month and intra-disease differences in reporting rates. With regard to reporting biases, only if under-reporting of chickenpox depended *systematically* on malaria rates, or vice versa, would these methods be inappropriate. However, there is no evidence in our

data of any such systematic error structure; the data come from routine surveillance. For example, chickenpox, having subclinical cases, may well be under-reported, but there is no reason to expect its month-to-month under-reporting rate to vary according to the other diseases.

3 Results

Table 1 shows that the total number of cases during the seven-year period is largest for malaria followed by influenza and chickenpox, and that the rank order is maintained throughout the year. Synchronously with the rainy seasons, malaria has two marked peaks, the first one in June, and a second, smaller, one in December. Influenza follows a similar pattern. Chickenpox incidence peaks in December, which is the middle of the school year, with a sharp decrease beginning in April. Figure 1 is a time series plot of the cases of all three diseases, on a logarithmic scale, and shows that influenza and malaria share a similar pattern.

Figure 2 (left panel) is the scatterplot of influenza cases vs. malaria cases, on log-log scale, with the OLS regression line ($R^2 = 46\%$). Clearly, the tendency is for months with more malaria cases to have more influenza cases, and vice versa. The right panel (influenza and chickenpox) has a slope that is shallower, and opposite in sign, and the scatter is greater ($R^2 = 10\%$). The scatterplots illustrate well that the simple correlation between cases of influenza and chickenpox is weaker than that between influenza and malaria.

Table 2 presents the Goodman-Grunfeld nonparametric analysis of disease comovement for influenza and chickenpox, and for influenza and malaria. The p-value for comovement between influenza and malaria is 0.000105. This is more conservative than the value obtained with a Pearson χ^2 test; interestingly, the p-value assuming a hypergeometric distribution (Fisher's 'exact' test) is about halfway between the two. We easily reject the null

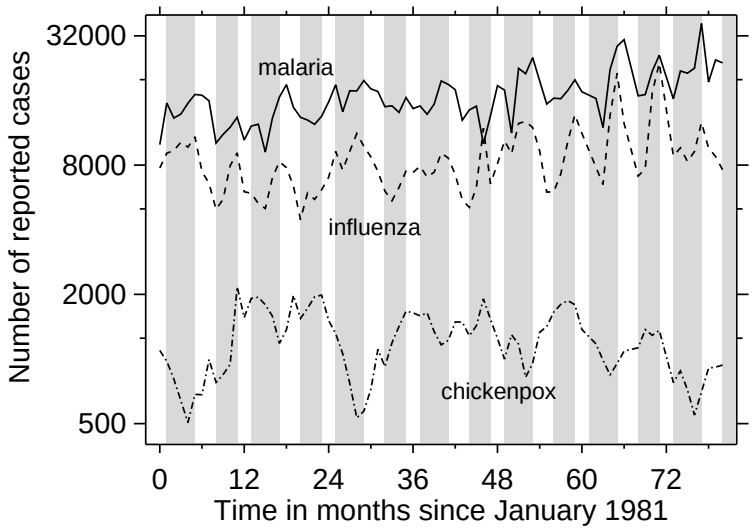

Figure 1: Time series plot of influenza, chickenpox and malaria cases, Burundi, 1981–87. Gray shading indicates twice-annual rainy seasons.

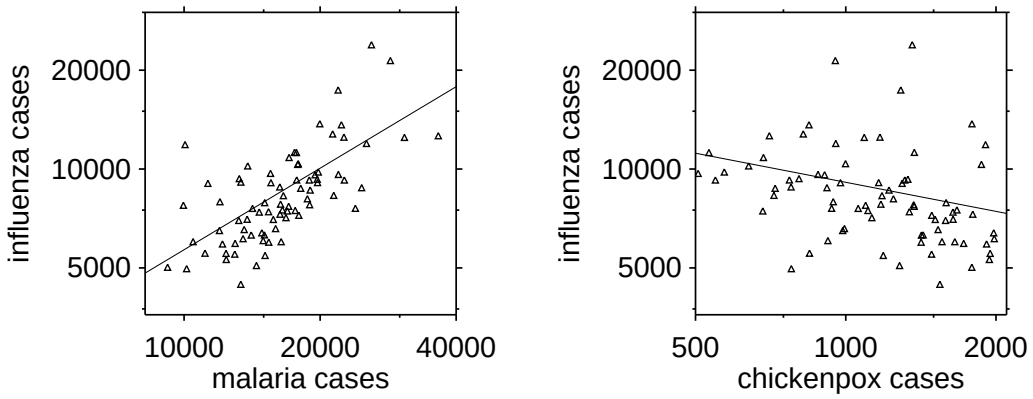

Figure 2: Influenza versus malaria (log-log), R^2=46% (left), and influenza versus chickenpox (log-log), R^2=10% (right). Burundi, 1981–87.

Table 2: Goodman-Grunfeld analysis of influenza, chickenpox, malaria: Burundi, 1981–87

	chickenpox		malaria	
influenza	Increases	Decreases	Increases	Decreases
Increases	19	20	30	9
Decreases	22	18	12	27
p-values:				
Pearson χ^2	0.58		0.000043	
Fisher's Exact Test	0.66		0.000087	
Goodman-Grunfeld	0.74		0.000105	

hypothesis of no comovement, and as is evident from figures 1 and 2, as well as from table 2, this is comovement not antimovement (the point being that the two-sided hypothesis test does not distinguish between the two, but that the graphs do). On the other hand, for influenza and chickenpox, we fail to reject the null hypothesis of no comovement (p=0.74), and in any case, even visual inspection of the 2×2 table leaves no doubt that these two times series do not co-move.

Although Burundi is geographically compact, it is ecologically heterogeneous, and one explanation worth ruling-out is that the three diseases are not geographically coincident. Hypothetically, if malaria is exclusively a rural disease and chickenpox predominantly an urban one, then there is not much logic to a country-wide comparison. Table 3 summarizes the Goodman-Grunfeld analysis, disaggregated by province. It gives the G-G p-value as well as the R^2 of the log-log case plot. In every province except one (Bururi), the G-G test favors the comovement of malaria and influenza (and in this province the test is not significant for either comparison), and the R^2 always favors malaria. Thus, we find no evidence that geographic aggregation effects are responsible for the overall finding.

Our case data are not laboratory-confirmed. Although respiratory symptoms would easily differentiate influenza from malaria (with fever being a commonality), and the rash would differentiate chickenpox, lab-confirmed results would clearly be more accurate. How-

Table 3: Goodman-Grunfeld analysis by province

Province	Test for comovement of influenza and: chickenpox G-G p-value	chickenpox R^2	malaria G-G p-value	malaria R^2
Bubanza	0.406	.0041	0.004	.43
Bujumbura	0.644	.027	0.272	.15
Bururi	0.223	.15	0.565	.2
Cankuzo	0.431	.01	0.001	.41
Cibitoke	0.789	.0048	0.390	.1
Gitega	0.089	.00012	0.001	.28
Karuzi	1.000	.0086	0.000	.016
Kayanza	0.934	.0069	0.076	.29
Kirundo	0.995	.0077	0.006	.29
Makamba	0.590	.2	0.576	.27
Muramvya	0.908	.0052	0.006	.15
Muyinga	0.217	.24	0.159	.44
Ngozi	0.571	.002	0.000	.28
Rutana	0.906	.012	0.003	.077
Ruyigi	0.940	.0049	0.024	.22
Whole Country	0.739	.1	0.000	.46

ever, in Africa, the representativeness of lab data would have to be scrutinized carefully. With high fever as a commonality of both syndromes, one possibility is that some malaria misdiagnosed as influenza drives the results. The lopsided numbers of the two diseases (cf. table 1) removes concern about the vice-versa bias. We do not believe that misdiagnosis drives our results, for two reasons. First, while fever is present in both cases, the clinical manifestations are saliently different. Major upper respiratory tract signs and symptoms are present in clinical influenza. Second, especially in Africa, malaria is often a default diagnosis for any febrile syndrome. Thus, the potential for error is that influenza cases are classified as malaria. The hypothetical concern is that spill-out from malaria could drive the result, but the realistic classification error would lead to spill-in to the malaria numbers.

4 Discussion

In the temperate regions, humidity patterns are broadly inversely related to the school calendar, though of course this is correlation not causation. Disentangling the effects of seasonal factors with school-year effects per se, is a challenge. The tropics present a unique laboratory in which to test theories of the effects of humidity on influenza virus transmission. Our data show that in Burundi, influenza incidence co-moves with malaria incidence, but not with chickenpox. Interpreting malaria as an indirect, but tightly-linked, measure of humidity, and chickenpox as a control for cyclical crowding factors, we infer influenza incidence to be more related to humidity.

This finding is in agreement with other work, which finds sporadic cases of influenza in Dakar during the first 6 and the last 3 months of the year, with an epidemic period during the hot, rainy season characterized by high relative humidity [13]. Accordingly, in Brazil, high levels of humidity coincide with influenza activity near equatorial regions [14]. This

is in contrast, however, with temperate regions, where influenza peaks during the winter, characterized by both lower temperatures and humidity levels [39]. Household contacts have been shown to be an important correlate of influenza transmission in temperate regions [11], but whether contact rates trigger influenza epidemics, as is thought to occur with chickenpox, is unclear. It cannot be ruled out that different factors govern influenza transmission in different contexts (i.e. the tropics versus temperate regions). Moreover, the superposition of many seasonal diseases in temperate winters make interpretation of single-disease seasonal patterns difficult; for example, chickenpox and influenza both peak in the winter. Fomite transmission may play a relatively larger role in influenza virus transmission in the tropics than in temperate regions. The explanation for this would be that humidity may enhance viral survival on surfaces even if it hampers airborne transmission (which is one explanation of experimental findings [4], though the animal model may also be sensitive to humidity).

Further work, including laboratory experiments with animal models, and epidemiological studies, is warranted to understand better the seasonal triggers of influenza globally. By linking diseases with known transmission factors (malaria and chickenpox) to the less-studied problem of influenza in the tropics, this study has demonstrated that an indirect method may provide information that would otherwise elude direct analysis. The present study lacks information on the age of the cases, and this would be potentially-useful data. Although we are highly confident in the robustness of malaria incidence data as an indirect measure of ambient humidity, meteorological measurement would also be a welcome addition.

In summary, our analysis suggests strongly that influenza incidence in Burundi is procyclical with humidity. All cyclical diseases in our dataset are not in-phase with one another, since chickenpox exhibits no co-movement with influenza, whereas malaria

and influenza exhibit strong comovements. This is in contrast to temperate regions where chickenpox and influenza both follow winter patterns. More investigation is warranted, but these results show that, at least with respect to humidity, the topics and temperate regions show diverging patterns. Regardless of the interpretations for the underlying mechanisms, the strength of our statistical findings suggest that, simply as an empirical matter, the comovement of incidence of influenza and malaria in Burundi is beyond doubt.

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