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Comparison of R_0 from Different Models for Dengue Fever in Pakistan

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***Abstract* – Dengue is an infectious disease, which is spread by a female mosquito Aedes aegypti. In order to ascertain the strength of this ailment in certain region, basic reproduction number R_0 is used for this purpose. We calculated R_0 by applying models to the confirmed cases of dengue fever for different hospitals of the Punjab, province of Pakistan. For the best calculated values of R_0 we will justify that, whether the disease is endemic, epidemic in Punjab or the region is disease free. In the last we suggest the role of different parameters to control the disease.**

***Keywords* – Vector Borne Disease, Reproductive Number, Dengue, Punjab.**

INTRODUCTION

Female mosquito Aedes aegypti is generally carrier of dengue fever. Disease is transmitted by a virus which has four serotypes Den-I, Den-II, Den-III and Den-IV. Transmission of disease needs human (host) and mosquito (vector) contact. When an infected vector bites susceptible human or susceptible vector bites infected human. After getting infection there is an intrinsic (in human) and extrinsic (in vector) incubation period of some days, then the transmission starts. In Pakistan Dengue fever is endemic since 1995 when the first case of disease was declared. For the last few years dengue fever has posed itself as a serious threat to the plethora of people, especially people in the Sindh province and in the province Punjab it has played a havoc and caused unspeakable damage to the general public health. In the period March 2010 to Jan 2012 Dengue fever remained epidemic in Punjab. Therefore It is very important to find the strength of disease in the Punjab province. The basic reproduction number R_0 is the common way to measure the strength of disease (Anderson and May 1991 , Dietz *et al* (1993)[1, 3]. It is defined as "primary number of infected cases which are produced by a single infected case in a susceptible population". For dengue fever to calculate R_0, four methods were introduced.

In the first method R_0 is estimated through the definition i.e the number of hosts basically infected by a single infectious case. This calculation requires entomological data i.e density of vector and number of bites. This remains mostly unknown or it is always difficult to find the exact data Koopman *et* al [8] In the second method Koopman *et* al [8] R_0 is calculated by final number of cases and the size of population in which the disease is epidemic. It becomes quite hard/sometime exactly onerous to determine them, for the reason of asymptomatic cases, or non declared cases this indicates under or over estimation than the actual. Reason thus the similarity of dengue fever symptoms with other diseases Guzman and Kauri 2002[7].

Third method considers the implicit transmission chain Wallinga and Teunis *et al* [12], But on the other hand it becomes increasingly difficult to estimate which infected whom. It is even more difficult when the declared number of cases do not match with real cases. In the fourth method, force of infection is calculated from the slope of the graph of daily number of cases plotted against cumulative number of cases .This is computed by least square linear fit of the data. This method depends on the daily number of declared cases (Marques et al , Massad *et* al [9,10]. In the methods M_1 and M_2 (see methodology) extrinsic and extrinsic incubation periods were not included this was the very reason that these methods could not better calculate the value of R_0.

METHODOLOGY

Many methods were used to calculate R_0 like (Marques *et* al) [9] (M_1). In their model they discussed the inverse of host viremia and force of infection. Later Massad *et al* [10] (M_2) discussed the impact of mortality of vector in addition to the factors discussed by Marques *et* al [9]

$$M_1 = \left(1+\frac{\Lambda}{\gamma}\right)$$

$$M_2 = \left(1+\frac{\Lambda}{\gamma}\right)\left(1+\frac{\Lambda}{\lambda}\right)$$

R_0 calculated by these methods could not give the better results because they did not consider the incubation period .Model presented by Favier c *et* al [4](M_3) considered the incubation periods both for the vector and human. Extrinsic incubation period and susceptibility of mosquito have been observed to depend on the temperature. Seasonal variation in temperature and rainfall are correlated with the strength of dengue infection. Later we will show that these factors affect the value of R_0.

Human population N_H is divided into three groups i.e susceptible human $S_H(t)$, infectious human $I_H(t)$ and recovered human $R_H(t)$, While vector is divided into two groups i.e susceptible vector S_V (t) and infectious vector I_V (t). Also $N_H = S_H + I_H + R_H$ and $N_V = S_V + I_V$. Transmission of dengue from one host to another via vector depends on many factors. Some of these factors like extrinsic and intrinsic incubation period and susceptibility of mosquito depends on the climatological conditions. Increase in the temperature and rainfall increases the strength of disease. It is because high temperature decreases the incubation period while the rainfall increases the vector breading sites. Incubation period in vector and humans is illustrated by fig (1).

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VIREMIA **Host # 1**

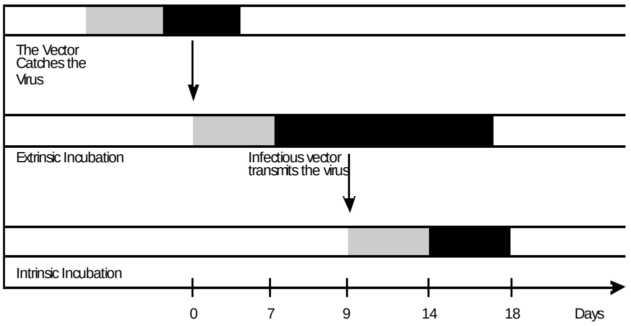
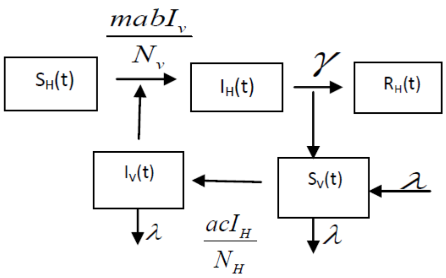


Fig.1. (Favier.C *et al*) Once the vector is infected it last to the rest of its life. Here extrinsic incubation period is taken as 7days. The intrinsic incubation remains for 5 days while the Viremia lasts for 4 days.

Block Diagram

Diagram below shows the susceptible humans infected by infectious vector and susceptible Vectors infected by humans. The rate of Infection of human by vector is $\frac{mabI_v}{N_v}$

And rate at which mosquito is infected by Human $\frac{acI_H}{N_H}$ is



Parameters

Parameters Signification	Range in control model
a Mean number of bites per day per vector and per host	0–0.5 day^{-1}
b Proportion of bites of infectious vectors on susceptible hosts leading to host infection	0-1
c Proportion of bites of susceptible vectors on viremic host, leading to vector infection	0-1
m Number of vectors by hosts	0-3
H_0 Initial proportion of susceptible hosts.	1
Λ Inverse of the duration of host viremia	0–0.5 day^{-1}
λ Mortality rate of the vectors	0–0.2 day^{-1}
τ_e Extrinsic (vector) incubation period	1-16 days
τ_i Intrinsic (host) incubation period	1-11 days

Mathematical Model

$$\frac{dS_H}{dt} = -mab\frac{S_H(t)I_V(t)}{N_V(t)} \qquad (1)$$

$$\frac{dI_H(t)}{dt} = mab\frac{S_H(t-\tau_i)I_V(t-\tau_i)}{N_V(t)} - \gamma I_H(t) \qquad (2)$$

$$\frac{dS_V(t)}{dt} = \lambda N_V(t) - ac\frac{S_V(t)I_H(t)}{N_H(t)} - \lambda S_V(t) \qquad (3)$$

$$\frac{dI_V(t)}{dt} = \exp(-\lambda\tau_e)\, ac\frac{S_V(t-\tau_e)I_H(t-\tau_e)}{N_H(t)} - \lambda I_V(t) \qquad (4)$$

Initially, in the case of epidemic, the infected number of accumulative cases can vary as

$I_H \propto \exp(\Lambda t)$ and $I_V \propto \exp(\Lambda t)$

and

Implies that

$I_H = H_0 \exp(\Lambda t) \qquad I_V = V_0 \exp(\Lambda t)$

Where Λ is the force of infection and H_0, V_0 are initial number of susceptible humans and vectors. Moreover it is assumed that non-Susceptible humans and vectors are *nigligible. So that* $S_H \approx N_H$ *and* $S_V \approx N_V$ then we can write

$$\frac{dI_H}{dt} = H_0\Lambda\exp(\Lambda t) \qquad (5)$$

$$\frac{dI_V}{dt} = V_0\Lambda\exp(\Lambda t) \qquad (6)$$

Using equations (5) and (6) in equation (2) we get

$$\frac{mabV_0\exp(t-\tau_i)N_H}{N_V} - \gamma H_0\exp(\Lambda t) = H_0\Lambda\exp(\Lambda t)$$

implies that

$$mabV_0N_H\exp(-\Lambda\tau_i) - (\gamma+\Lambda)H_0N_V = 0 \qquad (7)$$

Using equations (5) and (6) in equation (4) we get

$$\frac{acH_0N_V\exp\Lambda(t-\tau_e)\exp(-\lambda\tau_e)}{N_H} - \lambda V_0\exp(\Lambda t) = \Lambda V_0\exp(\Lambda t) \qquad (8)$$

Implies that

solving equations (7) and (9) we have

$$ma^2bc\exp-\lambda\tau_e = (\lambda+\Lambda)(\gamma+\Lambda)\exp\Lambda(\tau_e+\tau_i)$$

Implies

$$acH_0N_V\exp-(\lambda+\Lambda)\tau_e - (\lambda+\Lambda)V_0N_H = 0 \qquad (9)$$

$$\frac{ma^2bc\exp-\lambda\tau_e}{\lambda\gamma} = \left(1+\frac{\Lambda}{\lambda}\right)\left(1+\frac{\Lambda}{\gamma}\right)\exp\Lambda(\tau_e+\tau_i)$$

but

$$R_0 = \frac{ma^2bc\exp-\lambda\tau_e}{\lambda\gamma} \qquad (Degallier\ et\,al\ \ 2005)\ [2]$$

thus

$$R_0 = \left(1+\frac{\Lambda}{\lambda}\right)\left(1+\frac{\Lambda}{\gamma}\right)\exp\Lambda(\tau_e+\tau_i) \qquad (10)$$

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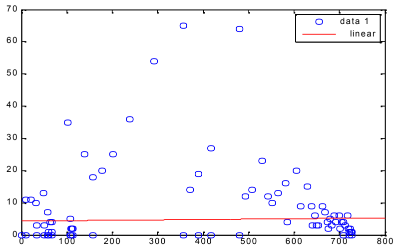
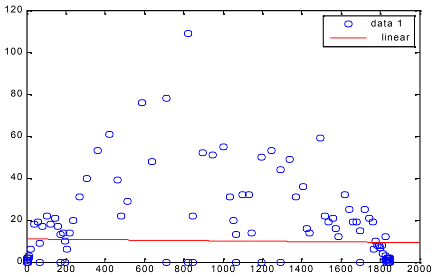
ESTIMATION OF R_0

From eq-10 to find R_0, first we find force of infection "□". One way to find the force of infection is to fit the cumulative number of cases. This is not most suitable way, because at the beginning of epidemic low level transmission of dengue disease affects the calculation of force of infection. On the other hand if we draw the daily number of infected cases against the cumulative number of cases then from the linear growth of the curve one can easily understand the exponential growth of cumulative number of cases, slope of this curve is the force of infection. Figure-3 shows the graph of daily number of dengue cases in different hospital of Punjab drawn against the cumulative number of cases. Slope of linear growth of the curve gives the force of infection "□" for five hospitals of Punjab.

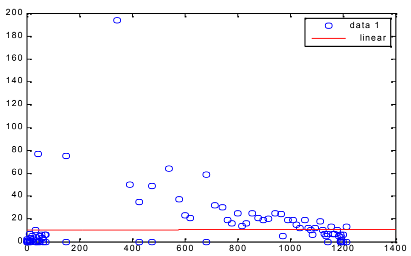
Fig (3).



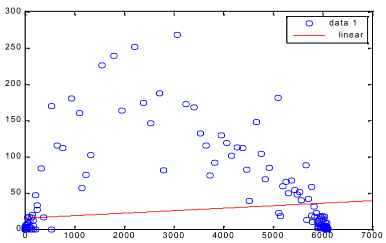
(a) Jinnah hospital



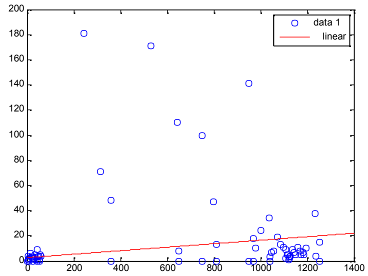
(b) I.P hospital



(c) Lahore hospital



(d) Mayo hospital



(e) Sir Ganga Ram hospital

Besides force of infection, we need four parameters τ_e ,τ_i , λ and γ. Two parameters which are related to host i.e. "τ_i" and mortality rate "γ" can be found from literature (MacBride & Bielefeldt-Ohmann 2000) [11]. γ^{-1} = 6 days and τ_i = 5 days. Extrinsic incubation period and mortality rate of vector are dependent on external temperature (Celsius) following Focks et .al (1993,1995)[5,6]. Favier C et .al (2006) [4] modeled them by the following equations:

$$\tau_e = 40.4\,\frac{298}{T}\exp\left[-7550\left(\frac{1}{298}-\frac{1}{T}\right)\right]$$

and

$$\lambda = -\ln\left[0.91\,\lambda_1(T)\,\lambda_2(P_{vd})\right]$$

Where "T" is the temperature in Celsius degrees and P_{vd} is vapour pressure in mbar. We model P_{vd} for relative humidity and temperature of Punjab (Table 1) during dengue epidemic year 2010-2011 as,

$$P_{vd} = 6.11\exp\left(17.3\,\frac{T}{T+237.3}\right)\left(1-\frac{R.H}{100}\right)$$

Where the function $\lambda_1 and\ \lambda_2\ are$

$$\lambda_1(T) = \begin{cases} T-5/5 & if\ \ 5<T<10 \\ 1 & if\ \ 10\le T\le 41 \\ 1-T-41/2 & if\ \ 41<T<43 \\ 0 & otherwise \end{cases}$$

and

$$\lambda_2 = \begin{cases} 1 & if\ \ P_{vd}<10 \\ 1-0.4(P_{vd}-10)/20 & if\ \ 10\le P_{vd}\le 30 \\ 0.6 & if\ \ P_{vd}>30 \end{cases}$$

Where "P_{vd} " is calculated from temperature and relative humidity (R.H). We use these models for relative humidity and temperature of Punjab data collected from Punjab metrological department during the epidemic year 2010-2011

Table 1: Monthly whether report of Punjab (2010-2011)

Month	V.P(m bar)	R.H (%)	Temp (C^0)
January	9.2	86	13.2
February	9.9	79.7	15.7
March	12.5	75.3	20.5
April	14	62.9	27

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May	15.4	53.3	31.7
June	21.8	61.7	33.6
July	29.8	81.7	31.3
August	31	85.8	30.7
September	25.5	82.5	29.6
October	17.5	80.1	25.7
November	13.2	84.6	20.1
December	11.5	86.9	14.8
Average	15.5	76.7	24

Table 2 : Values of R_0 from different models i.e M_1, M_2, M_3 for different hospitals of Punjab

Epidemic	^	T(^{0}C)	R.H(%)	γ	τ_e	M_1	M_2	M_3
Jinnah Hospital	0.028476	24.5	76.7	0.2108	12.3798	1.1709	1.3290	2.1806
I.P Hospital	0.014569	24.5	76.7	0.2108	12.3798	1.0874	1.1626	1.4976
Lahore Hospital	0.01553	24.5	76.7	0.2108	12.3798	1.0932	1.1737	1.5376
Mayo Hospital	0.01735	24.5	76.7	0.2108	12.3798	1.1041	1.1950	1.6155
Sir Ganga Ram Hospital	0.013927	24.5	76.7	0.2108	12.3798	1.0836	1.1552	1.4715

Discussion

Link between R_0 and force of infection "□" are dependent on the nature of epidemics. Estimate of R_0 and "□" is adapted to vector borne epidemics which are characterized with extrinsic and intrinsic period pertaining to incubation of dengue. Value of R_0 by M_3 is greater than those estimated by methods suggested before i.e M_1 and M_2 these methods did not consider incubation periods. There exist a lag between incubation period at which a host is viremic and the times of apparition of secondary cases from that host ultimately leads to a slower increase in the number of cases as it has been indicated by Wearing *et al* (2005)[13]. There are other factors too, which are likely to affect the link between the force of infection and the reproductive rate like, age dependent susceptibility, varied distribution of incubation and time of recovery. Here Incubation period is being assumed fixed and given recovery time exponentially distributed. Scanty information is there about these points hence no model refinement can be performed. Proposed method give the advantage of being independent from the strain implied. The strain chiefly influences the probability of virus transmission at the time of bite (parameters b and c) and the proportion of symptomatic cases. Our estimation of R_0 is not influence by these factors because contacts are taken to be homogeneous Favier et al (2005). This is not the case of dengue epidemics. Spatial structure of contacts strongly influences the course of epidemics. In the initial stage the affect is small and link between the force on infection and reproductive rate is not vitally affected (Anderson and May 1991, Favier et al, 2005). Pure exponential initial growth assumption was an acceptable approximation to estimate the reproduction Number. The city-wide epidemic data was gained from the hospitals (Mayo Hospital, I. P Hospital, Sir Ganga Ram Hospital, Lahore Hospital). Such an assumption was not sufficient to estimate the reproduction number for local dengue in Punjab Province. Vector population is taken as constant in the model. This is not realistic in tropical climates where there is perceptible change in Mosquito growth during a year. Early exponential stage could be evidenced. That shows in the early epidemics mosquito growth (couples with other climate related factors) are constant to estimate a mean value R_0.

Value of R_0 for the Punjab epidemics reaches for greater values must be taken into account cautiously. More studies in depth on the Punjab epidemics are quiet essential to be conducted to find out the basis of discrepancy, for instance it comes out from a different immunological status of Punjab population contrasted with the population of other cities. The very steep epidemic start could be connected to external factors, like dengue importation from other provinces and cities. Model of extrinsic incubation period can be overestimated in relatively low temperature. Two factors can explain why such important outbreaks are finally constrained. The first is that, after the start of epidemic contact heterogeneities between vectors and hosts (spatial effects and structures of contacts between both populations, because of limited range of Ades aegypti) decreases course of epidemics, as compared to homogeneous contact assumption. Second and very essential factor is environmental factors, changing climate with a modulation of vector lifespan, duration of gonotrophic cycles and incubation period, temperature and humidity or with a variation of emergence of adults with precipitation. They can be man related to control measures set during the epidemic.

Conclusion

As we know that force of infection influence R_0. But force of infection depends on the nature of epidemic. There are other factors which effect the force of infection i.e variation in age, the susceptibility, incubation period (here incubation period is fixed), recovering time. But it is very very difficult to get true data about above factors. The method M_3 is independent of these factors because above strain mainly influence the virus transmission time. In the early epidemic mosquito population and other climate factors are constant enough to calculate R_0. From table-2 it can be seen that by considering the incubation period the value of reproduction number is well estimated. Obviously after incubation period the number of infected vector and human increases which ultimately increases the force of infection. There can be other factors which affect the force of infection as pointed out Wearing *et al*[13]. These are different distribution of incubation and recovering time. But very trivial information is available about them.

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Therefore incubation period is assumed fix and contact rate is taken homogeneous. From Table-2 the best estimation of R_0 is M_3. Value of R_0 calculated from M_1, M_2, and M_3 for all five hospitals of Punjab the situation is alarming as $R_0 > 1$. It means that in Punjab the Dengue disease is endemic. Reproduction number depends on m (vector from human), the parameters "b" and "c". R_0 increases with the increase in m, b and c. In the absence of dengue vaccine public health control depends on reduction of reproduction number which is reduced by decreasing the parameters b,c and m. This can be done by reducing the vector breeding sites, decreasing the life span of vector, reducing the mosquito biting rate by quarantine and by targeted spray on larval places.

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