Review

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Mathematical Modeling of Viral Epidemics: A Review

Pratip Shil

National Institute of Virology, 130/1Sus Road, Pashan, Pune – 411021, India

Mathematical models to describe transmission and propagation of diseases have gained momentum over the last hundred years. Formulated mathematical models are currently applied to understandthe epidemiology of various diseases including viral diseases viz Influenza, SARS, measles, etc. With the emergence of advanced computing tools, designing mathematical models and generating simulations (numerical solutions) have become feasible. There is an enormous scope for using mathematical models in studying epidemiology of viral diseases through transmission dynamics of outbreaks and in evaluating or predicting the effects of interventions and vaccinations. The influenza pandemic of 2009 and the recent Ebola epidemics of 2014-15 have generated renewed interest in mathematical modelling of epidemics. Here we present a review of the various mathematical models and their applications in the study of virus driven epidemics.

INTRODUCTION

Mathematics has made significant inroads in biology and medicine with mathematical theories and models being used to study and understand various processes or phenomenon including transmission dynamics of diseases (Abidor*et al*., 1979; Anderson, 1991; Aronson *et al*., 1975; Ball *et al*., 2010; Beirne, 1975; Bowman *et al*., 2005; Carrillo *et al*., 2010; Chowell *et al*., 2006a; 2006b; Cohen *et al*., 2004; Hodgkin *et al*., 1952; Kermack *et al*., 1927; Krassowska *et al*., 1994; Meena *et al*., 2010; Michaelis *et al*., 1913; Mishra *et al*., 2010; Shil *et al*., 2008; Smith *et al*., 2004; Yousfi *et al*., 2011). The progress of mathematical sciences including geometry, algebra and analyses over the last few centuries has enriched different branches of biological sciences. Simultaneously, conceptual and scientific challenges from biology have enriched mathematics by leading to innovative thought and development of novel approaches to mathematical theories. Several pioneering examples include age structure of stable populations by Euler 1760 AD, correlation coefficient by Pearson 1903 AD, Markov chains and

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***Corresponding Author:** Pratip Shil, National Institute of Virology, 130/1Sus Road, Pashan, Pune – 411021, India.
Email: shil.p@gov.in

statistics of language by Markov 1906, dynamics of interacting species by Lotka 1925, game theory by Neumann and Morgenstern 1953, diffusion for gene frequencies by Kimura 1994 (Cohen, 2004). The pandemic caused by the novel Influenza A/H1N1 2009 and more recent Ebola epidemic have resulted in a renewed interest in mathematical modelling of epidemics (Chowell *et al*., 2014; Fraser*et al*., 2009; Lewnard *et al*., 2014).

Mathematical theories and models are used to analyze both data and new ideas in epidemiology. The process of scientific progress is to observe a phenomenon, generate a hypothesis and design experiments to test the hypothesis. Experiments in epidemiology are difficult to design, with serious ethical issues. A mathematical model, on the other hand, is a description of a phenomenon or situation based on a hypothesis. The general process involve certain assumptions on disease propagation, formulation of the assumptions in mathematical terms and translation into a mathematical problem. The mathematical problem then becomes the model for the epidemic. The numerical solution of the models can be obtained by computer simulations and the outputcompared with the real data. Also, the real data can be fitted to a model to deduce several parameters (Brauer, 2009).

The first mathematical model in epidemiology was developed to study the variolation against small pox in increasing life expectancy by Bernouli (Brauer, 2009; Bernouli, 1760)**.** The foundation of mathematical epidemiology was laid by the contribution of several biologists and physicians as P. D. Enko, W. H. Hamer, Sir R. A. Ross, A. G. McKendrick and W.O. Kermack. The works of Ross on malaria (Ross, 1911) and Kermack and McKendrick (Kermack *et al*., 1933) are considered as landmarks in the development of mathematical epidemiology. Ross, based on his extensive research on malaria in India, showed that the disease was spread by the mosquitoes and developed a model describing the transmission (Ross, 1911). He predicted from this model that reduction of the mosquito population would effectively control the malaria epidemic in a geographical area. Further, several disease specific modelling studies including measles, gonorrhea, AIDS, leprosy (Allen *et al*., 1990; Anderson, 1991; Castillo–Chavez *et al*., 1989; Gupte *et al*., 2000; Hethcote *et al*., 1984; Meima *et al*., 1999).

The concept of basic reproduction number was developed in the works of

Kermack and McKendrick (Kermack, *et al.* 1933). The authors analysed disease propagation in: i) diseases where the infected person recovers and gets conferred immunity against the causative agent (viral diseases) and ii) diseases with recovery but without conferred immunity against the causative agent (bacterial and sexually transmitted diseases). The basic reproduction number, universally denoted as R_0, defines the average number of secondary infections generated by an average infective introduced into a wholly susceptible population. The greater the R_0, the more intense is the transmission and hence more severe is the epidemic. The concept of R_0 is the central idea in mathematical epidemiology as it is vital for prediction or description of transmission dynamics of any epidemic.

The current literature review is a compilation of various mathematical modelling studies on epidemic spread of air-borne and vector borne viral diseases. The review by Zhang *et al*. (2001) is referred to for plant viral epidemics, as it is not within the scope of the current review.

Models for air-borne diseases

1) Susceptible - Infectious - Recovered (SIR)

The first mathematical model used to describe an influenza epidemic was developed by Kermack and McKendrick, popularly known as Susceptible-Infectious-recovered or SIR model. It assumes the introduction of one infected individual into a population where the members are not previously exposed to the pathogen and are hence all susceptible (S). Each infected individual (I) transmits to susceptible members of the population with a mean transmission rate β. At the end of the infectious period, the individual recovers and is considered as Recovered (R) member of the population. If the mean recovery rate is α, then the mean transmission period in any individual is given by 1/α. Fig. 1 describes schematically the SIR model of disease transmission. The set of differential equations describing the transmission as per the basic SIR model is given by

$$\frac{dS(t)}{dt} = -\beta S(t) I(t)$$

$$\frac{dI(t)}{dt} = \beta S(t) I(t) - \alpha I(t)$$

$$\frac{dR(t)}{dt} = \alpha I(t) \qquad \text{(Eqn. 1.1)}$$

Here, *S(t)* and *I(t)* denote the numbers of individuals in the Susceptible and Infectious states respectively at any time *t*. The rates of change of *S(t)* and *I(t)* with time are denoted by the derivatives *dS(t)/dt* and *dI(t)/dt* respectively. The total

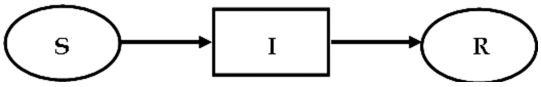

Figure 1. The schematic diagram of the SIR type transmission model. S, I and R denote Susceptible, Infective and Recovered /removed categories of the population.

population is considered constant and is given by $N = S(t) + I(t) + R(t)$, with no one coming in or leaving the system.

The number of susceptible individuals $S(t)$ decreases as the number of incidences (i.e., Infectives $I(t)$) increase. The epidemic peaks then declines as more and more individuals recover and stop transmitting the disease. Considering everyone initially to be susceptible (i.e., at t=0, $S(t) = N$), a newly introduced infected individual can infect on the average $\beta N/\alpha = R_0$individuals. This is the basic reproduction number, R_0. In other words, R_0 describes the average number of secondary infections generated by one infectious individual when introduced into a fully susceptible population. The severity of the epidemic and rates of increase depend on the value of the basic reproduction number. If $R_0 > 1$, then the epidemic will continue. If $R_0 < 1$, then the epidemic will die out. R_0 can be calculated form the growth rate of the epidemic (r) obtained from the cumulative incidences data in the initial growth phase of the outbreak, as:

$$R_0 = \left(1 + \frac{r}{\alpha}\right) \quad \text{(Eqn. 1.2)}$$

The numerical solutions of the ordinary differential equations (Eqn1.1) can be obtained with suitable boundary conditions (appropriate for the disease) using computer simulations. The model has been used to explain the transmission of measles in New York, in 1962 and also repeated outbreaks of the disease between 1930 and 1962 (Anderson, 1991).

The SIR model can be extended to explain occurrence of repeated epidemics in one place due to a pathogen by considering the demographics i.e., addition and removal of individuals from a population through birth and death, respectively. Considering B to be the birth rate per unit time, and a mortality rate (per capita) μ, the Eqn1.1 can be modified as

$$\frac{dS(t)}{dt} = B - \beta S(t) I(t) - \mu S(t)$$

$$\frac{dI(t)}{dt} = \beta S(t) I(t) - \alpha I(t) - \mu I(t) \quad \text{(Eqn. 1.3)}$$

Such modification of the basic SIR model has been used to explain the occurrence of Measles (Anderson 1991). The effects of weather or seasonal variations in human behavior may affect the transmission of a disease. These effects can be incorporated by assuming a transmission rate to be a periodic function in time. A crude

approximation of seasonally forced transmission rate is

$$\beta(t) = \beta_0(1 + A\cos 2\pi t) \quad \text{(Eqn. 1.4)}$$

where, A is the constant defining the amplitude of seasonal variation ($0 \leq A \leq 1$).

The modified SIR models have also been used to explain the dynamics of transmission of various diseases like the measles **(**Allen *et al*., 1990) and influenza (Dushoff *et al*., 2004; Stone, 2007). The SIR model has also been suitably modified to represent or predict spatio-temporal dynamics of disease especially, Influenza outbreak in the erstwhile USSR (Rvachev,1968) and also to incorporate the effects of air travel on influenza pandemics (Baroyan *et al*., 1971; Coburn *et al*., 2009; Rvachev *et al*., 1985).

2) Susceptible - Exposed - Infectious-Recovered (SEIR)

In case of certain infectious diseases, an incubation period or exposed state in an individual following transmission (receiving the causative agent) and till the onset of the symptoms is observed. Hence, the simple SIR model cannot effectively describe transmission of such diseases. Hence, mathematical model should account for the exposed state or the latent state, giving rise to development of the Susceptible- Exposed-Infectious-Recovered or SEIR model.

The SEIR model also assumes introduction of one infected individual into a population where the members are not previously exposed to the pathogen and are hence all susceptible (S). Each individual who received the causative agent (pathogen) exist in the Exposed or Latent state (E) during which he/she is incubating the virus or bacteria but the does not transmit the infection to anyone. With the onset of the symptom, the same individual makes a transition to the Infectious state and is considered as an infected individual (I). If κ be the rate of transition from the Exposed state to the Infectious state, then duration of the mean exposed period or latent phase is $1/\kappa$.Infected individual transmits tosusceptible members of the population with a mean transmission rate β. At the end of the infectious period, the individual recovers and is considered as Recovered (R) member of the population. If the mean recovery rate is α, then the mean transmission period in any individual is given by 1/α. Fig. 2 describes schematically the SEIR model of disease transmission. Considering the constant population size N= S + E + I + R, the set of

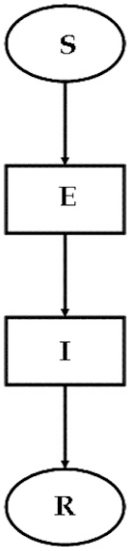

Figure 2. The schematic diagram of the SEIR type transmission model. S, E, I and R denote Susceptible, Exposed (latent), Infective and Recovered /removed categories of the population, respectively.

differential equations describing the transmission as per the basic SEIR model is given by

$$\frac{dS(t)}{dt} = -\beta S(t) I(t)$$

$$\frac{dE(t)}{dt} = \beta S(t) I(t) - \kappa E(t)$$

$$\frac{dI(t)}{dt} = \kappa E(t) - \alpha I(t)$$

$$\frac{dR(t)}{dt} = \alpha I(t) \qquad \text{(Eqn. 2.1)}$$

If we assume that a fraction f of the individuals leaving the infectious state at time *t* recover while the fraction (1-f) die due to disease, then the Eqns. 2.1 can be modified as :

$$\frac{dS(t)}{dt} = -\beta S(t) I(t)$$

$$\frac{dE(t)}{dt} = \beta S(t) I(t) - \kappa E(t)$$

$$\frac{dI(t)}{dt} = \kappa E(t) - \alpha I(t)$$

$$\frac{dN(t)}{dt} = -(1-f)\alpha I(t) \qquad \text{(Eqn. 2.2)}$$

It should be noted that in this case the population is not constant but decreases as more members of the population succumb to the disease. Considering a scenario of no removal by death, the basic reproduction number can be evaluated based on the growth rate of the initial phase of an outbreak for the simple SEIR model as follows.

The growth rate of the epidemic (*r*) can be calculated from the estimates of cumulative number of confirmed infections (y) and the estimated start date and size of the outbreak (t_0 and y_0), respectively, using the equation (Fraser *et al.*, 2009), $y = y_0 e^{r(t-t_0)}$ (Eqn. 2.3)

The basic reproduction number (R_0), is determined using the formula:

$$R_0 = \left(1+\frac{r}{\alpha}\right)\left(1+\frac{r}{\kappa}\right) \qquad \text{(Eqn. 2.4)}$$

with the mean infective period $1/\alpha$ and mean incubation period $1/\kappa$. This gives a more accurate estimation of the R_0compared to the SIR model, where the latent phase was not considered. This is best explained with the help of an example. Gurav *et al*. (2010) has reported about the novel influenza A/H1N1 2009 (Swine flu)

outbreak in a residential school in Panchgani, Maharashtra. Based on the epidemiologic data for the outbreak, Shil *et al*.(2011) derived the intrinsic exponential growth rate (r) to be 0.2341 per day. Assuming the mean incubation period to be 1.5 days and mean infectious period to be 4 days, the R_0 was estimated to be 2.61 (as per Eqn. 2.4). Similar higher values of R_0 and intense transmissions were also observed in various countries for communities with close clustering of people such as village and schools (Guinard *et al*., 2009; Smith *et al*., 2009; WHO, 2009).

The SEIR model with suitable adaptations has been widely used for various diseases including influenza, chicken pox and SARS (Deguen *et al*., 2000; Riley *et al*., 2003). Deguen *et al*. (2000) analysed the seasonal pattern of chicken pox epidemic in France by fitting SEIR model with a periodic contact rate function to weekly chicken pox incidence data collected from 1991-1996. Both the models, assuming either continuous or piecewise constant periodic function, gave reasonable fit to the incidence data and yielded estimates of incubation and infectious periods consistent with the clinically or serologically estimated values. Wang *et al*. (2006) have adapted the SEIR model with a time dependant transmission rate (contact per infectious person per day) for describing the SARS outbreak in Beijing city. The SEIR solution precisely matched the epidemiology data. To study the transmission dynamics of the SARS outbreak in Hong Kong (2003), Small and colleagues (Small and Tse, 2005a; 2005b) adapted the SEIR concept in a 'Small World Model' where transmission was allowed within population clusters and between a random number of geographically distant clusters. Transmission was allowed only between linked nodes/ clusters. This concept could effectively describe the SARS outbreak of 2003 as the computer simulations matched the recorded data.

3) Susceptible - Exposed - Infectious - Asymptomatic - Recovered (SEIAR)

A simple model of disease propagation involving asymptomatic individuals in the population in a scenario without any interventions, that is, an untreated Susceptible - Exposed - Infective-Asymptomatic-Recovered model is explored. In the model the individuals were classified as: Susceptible (*S*) – those who did not have any immunity to the disease; Exposed (*E*) or latent – those

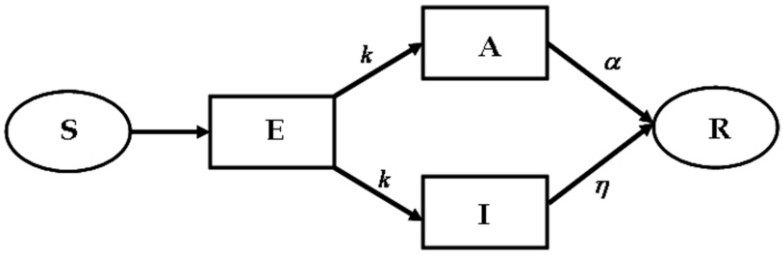

Figure 3. The schematic diagram of the SEIAR type transmission model. S, E, I, A and R denote Susceptible, Exposed (latent), Infective, Asymptomatic and Recovered /removed categories of the population, respectively.

exposed to the virus and incubating it prior to the development of symptoms; 'Infectives' (I) – symptomatic and infectious; Asymptomatic (A) – those testing positive in serological tests/blood tests for the disease, but had no symptoms (were assumed to be partially infectious); and recovered population (R). A flow diagram for the SEIAR model is given in Fig. 3. Following assumptions are made where S, E, I, A, R, denote the numbers of individuals in the Susceptible, Latent (or exposed), Infective, Asymptomatic and Recovered compartments respectively, with the total population size at all times given by $N = S(t) + E(t) + I(t) + A(t) + R(t)$, as: i) Total population at the initial stage was susceptible with no members having immunity through vaccination or any previous exposure. One infective was introduced. ii) There is no transmission from individuals at the Latent (Exposed) state. iii) A fraction p of the latent (E) individuals proceed to Infective (symptomatic) I compartmentat the rate k. The remaining fraction (1-p) goes to the asymptomatic compartment A at the same rate k. iv) The study population is considered constant and no consideration has been made for the addition or removal of individuals. v) Asymptomatic individuals have a reduced capacity to transmit the disease. Let 'q' be the factor that decides reduction in transmissibility of the asymptomatic individuals ($0 < q < 1$) (Poddar *et al*., 2010; Shil *et al*., 2011). vi) Assuming homogeneous mixing within the population, the average member of the population made contact sufficient to transmit infection to βN others per unit time, where β is the transmission rate. vii) A fraction α of the infective individuals and a fraction η of the asymptomatic individuals moved to recovered class per unit time. viii) No restrictions on human behaviour (such as quarantine, wearing of masks) or interventions (as preventive medicine) are imposed.

The transmission process is described by the following set of ordinary differential equations (ODE):

$$\frac{dS}{dt} = -\beta S(I + qA)$$

$$\frac{dE}{dt} = \beta S(I + qA) - kE$$

$$\frac{dI}{dt} = pkE - \alpha I$$

$$\frac{dA}{dt} = (1-p)kE - \eta A$$

$$\frac{dR}{dt} = \alpha I + \eta A$$

$$\frac{dC}{dt} = \alpha I \qquad \text{(Eqn. 3.1)}$$

Here, *C* denotes the cumulative number of infectives.

Also, all variables are positive at all times ($0 < t < \infty$) (Poddar *et al*., 2010; Shil *et al*., 2011).

The untreated SEIAR model with modifications has been adapted to explain the Influenza A/H3N2 outbreak in Tristan da Cunha 1971 (Mathews *et al*., 2007). Recently we have used this model to explain the transmission dynamics of the Swine flu outbreak at a residential school setting in Panchgani, Maharashtra, India (Shil *et al*., 2011). Analyses of epidemiological data obtained from the outbreak revealed that close clustering within population resulted in high transmissibility with basic reproduction number R_0= 2.61 and transmission rate (β) being 0.001566. The doubling time (the time period in which the size of the outbreak doubles) as calculated from t_d = *ln (2/r)*, where *r* is the exponential growth rate of the epidemic (Shil *et al*., 2011; Wallinga*et al*., 2007), was found to be 2.14 days. The study provided estimates for various parameters for the outbreak such as the partial infectiousness and its duration in the asymptomatic cases. Such parameters were difficult to determine by clinical observations. The study also enabled qualitative assessment of the effect of control measures (behavioural interventions, etc) in controlling the outbreak in a closed population.

4) Complex SEIAR (hospitalization)

We now move on to explore how to incorporate the effects of interventions such as hospitalization into the SEIAR model. Chowell *et al*. (2006) described a complex SEIAR incorporating hospitalization of a fraction of the Infectives. As in the SEIAR model, the members of the population were classified into S, E, I, A, R with J(t) and D(t), in addition denoting the fraction hospitalized and dead respectively, described in Fig. 4.

Initially the entire population is susceptible. It is assumed that an Asymptomatic individual transmits

Figure 1: Genetic poly

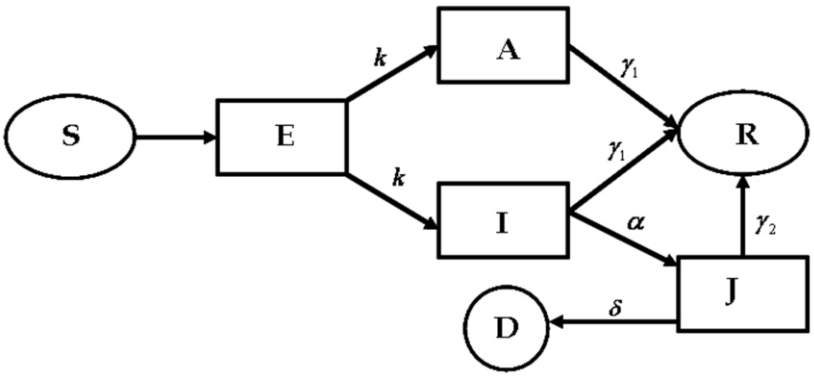

Figure 4. The schematic diagram of the SEIAR type transmission model. S, E, I, A, J, R and D denote susceptible, exposed (latent), infective, asymptomatic, hospitalized (severe cases), recovered and dead categories of the population, respectively.

disease with a reduced transmissibility. Let q ($0 < q < 1$) be the factor that decides the reduction in transmissibility of the Asymptomatics. Susceptible individuals contacting the virus/causative agent move to the latent class at a rate)

$(I(t) + J(t) + qA(t)) / N(t)$,

where β is the transmission rate.

The total population at any time t is given by $N = S(t) + E(t) + I(t) + A(t) + J(t) + R(t)$. Assuming homogeneous mixing of the population and that $J(t)$ are equally infectious as the I(t), the probability of a random contact with the Infective individual is given by,

$(I(t) + J(t) + qA(t) / N(t)$

A fraction ρ of the latent individuals ($0 < \rho < 1$) develop symptoms and become Infective at the rate κ and the rest ($1-\rho$) progress to become asymptomatic A(t) also at the same rate κ. Asymtomatics proceed to recovered R(t) class at the rate γ_1. The infectious individuals are diagnosed and hospitalized at rate α, while some recover with hospitalization at rate γ_2 ordie at the rate δ. The transmission is described by the following set of differential equations:

$$\frac{dS}{dt} = \mu N(t) - \frac{\beta S(t).(I(t) + J(t) + qA(t))}{N} - \mu S(t)$$

$$\frac{dE}{dt} = \frac{\beta S(t).(I(t) + J(t) + qA(t))}{N} - (\kappa + \mu) E(t)$$

$$\frac{dA}{dt} = \kappa(1 - \rho)E(t) - (\gamma_1 + \mu) A(t)$$

$$\frac{dI}{dt} = \kappa \rho E(t) - (\alpha + \gamma_1 + \mu) I(t)$$

$$\frac{dJ(t)}{dt} = \alpha I(t) - (\delta + \gamma_2 + \mu) J(t)$$

$$\frac{dR(t)}{dt} = \gamma_1 (A(t) + I(t)) + \gamma_2 J(t) - \mu R(t)$$

$$\frac{dD(t)}{dt} = \delta J(t)$$

$$\frac{dC(t)}{dt} = \alpha I(t) \qquad \text{(Eqn. 4.1)}$$

Here, μ has been considered to be the

rate of birth as well as the rate of natural death in the study population. The cumulative number of confirmed infections is given by $C(t)$. Epidemic data obtained from the Spanish flu pandemic in Geneva was used for fitting to this model and determined the parameters β, γ_1 ,q, α, etc.

The SEIR and SEIAR models had been extended by incorporating various parameters and accounting for public health interventions, behavioral changes or restrictions like school closure, travel restrictions or quarantine, etc in containing spread of viral diseases like influenza (Arino *et al*., 2006; Ballesteros *et al*., 2009; Baroyan *et al*., 1971; Bootsma *et al*., 2007; Chauchemez, 2008; Chowell *et al*., 2006;2007; Coburn *et al*., 2009; Fergussion *et al*., 2006; Longini *et al*., 2005; Mills *et al*., 2004; Sattenspeiel *et al*., 2003;). The effects of vaccination in controlling of the influenza epidemics was also studied (Coburn*et al*., 2009; Galvanic*et al*., 2007; Vardavas *et al*., 2007). The model presented by Longini *et al*. (2005) to describe the influenza (H2N2) pandemic of 1957-58 provided discrete-time simulations based on detailed contact structure. With the advent of the vaccine against novel influenza A/H1N1 (2009), mathematical modelling approach has also been used to decide the effective dosage (Nishiura *et al*., 2009).

Modelling Vector–borne diseases

In case of vector borne diseases transmission depends on several factors including the population of vectors (mosquitoes) and the population of human hosts along with the infected members (within each population) and the nature of vector-host interactions. The first mathematical model for vector borne disease was given by Ross and McDonald. This was improvised upon and adapted for various mosquito borne diseases such as Dengue over the ages (Esteva *et al*., 1999; Kongnuy *et al*., 2011). Described below is a simple model for transmission of mosquito borne disease (Kongnuy *et al*., 2011).

Let us assume that the total populations of both humans and mosquitoes are constants and denoted by H and M, respectively. Let $X(t)$ and $Y(t)$ denote the numbers of infected humans and mosquitoes at any time t, respectively. Let α be the rate of biting on humans by a single mosquito (number of bites per unit time). Then the number of bites on humans per unit time per human is α /H. If b is the proportion of infected bites on humans that produce an infection, the interaction

between the infected mosquitoes $Y(t)$ and the uninfected humans $H - X(t)$ will produce new infected humans of $(\alpha/H)b[H - X(t)]Y(t)$. Let the incubation period in a human be of duration τ_1, then it is possible that some individuals might recover or do not get the disease during this incubation period. Thus, of those individuals infected τ_1 unit times ago, only a proportion

$$(\frac{\alpha}{H})b[H - X(t-\tau_1)Y(t-\tau_1)]\exp(-r\tau_1)$$

is infectious at the present time t, where r is the per capita rate of recovery in humans so that $1/r$ is the duration of the disease in humans. Therefore, the equation for the rate of change in the number of infected humans is

$$\frac{dX}{dt} = -rX(t) + \left(\frac{\alpha}{H}\right)b[H - X(t-\tau_1)]Y(t-\tau_1).\exp(-r\tau_1)$$

(Eqn. 5.1)

Let μ be the per capita rate of mortality in vectors then, $1/\mu$ is the life expectancy of vectors. If the incubation interval of the pathogen in the mosquito has duration τ_2, and c is the transmission efficiency from human to mosquito, then we have the equation for the rate of change in the number of infected mosquitoes as:

$$\frac{dY}{dt} = -\mu Y(t) + \left(\frac{\alpha}{H}\right)c\,X(t-\tau_2)[M - Y(t-\tau_2)].\exp(-\mu\tau_2)$$

(Eqn. 5.2)

If $x(t)$ and $y(t)$ are the proportion of infected humans and mosquitoes at time t, respectively, and m be the number of mosquitoes per human host, then

$$x(t) = \frac{X(t)}{H},$$

$$y(t) = \frac{Y(t)}{M}$$

and

$$m = \frac{M}{H}.$$

Then, we can define the dynamics of the disease by the following set of differential equations:

$$\frac{dx}{dt} = rx(t) + \alpha\, b\, m(1 - x(t-\tau_1))y(t-\tau_2).\exp(-r\tau_1)$$

$$\frac{dy}{dt} = \mu\, y(t) + \alpha\, c\, mx(t-\tau_1)(1 - y(t-\tau_2)).\exp(-\mu\tau_2)$$

(Eqn. 5.3)

The model has been used by Ruan *et al*. (2008) for analyses of malaria and adapted by Massad and coworkers (Massad*et al*., 2010) for description of Dengue transmission. Ruan *et al*. (2008) have estimated the basic reproduction number R_0 by different methods including an adaptation of this model. For a vector borne disease, R_0 may be considered as the number of persons who would be infected from a single person initially infected by a mosquito. According to this model the basic reproduction number is estimated as:

$$R_0 = \frac{\alpha^2 bcm}{r\mu}e^{-r\tau_1}e^{-\mu\tau_2}$$

Considering a primary case with a recovery rate of r, the average time spend in an infectious state is $1/r$. During this

time, since the incubation period in humans has duration τ_1, the average number of mosquito bites received from m susceptible mosquitoes, each with a biting rate α, gives a total of $\frac{\alpha cme^{-r\tau_1}}{r}$ mosquitoes infected by the primary human case. Each of these mosquitoes survives for an average time $1/\mu$ and with another incubation period τ_2 in mosquitoes, makes a total of $\frac{\alpha cme^{-\mu\tau_2}}{\mu}$ infectious bites. The total number of secondary cases is thus estimated to be $\frac{\alpha^2 bcm}{r\mu} e^{-r\tau_1} e^{-\mu\tau_2}$ which is (2). The parameter α appears twice in the expression because the mosquito biting rate controls transmission from humans to mosquitoes and also from mosquitoes to humans.

This model has been used for modelling epidemics driven by arboviral diseases. Massad *et al*. (2010) adapted the model with suitable modifications for estimating the R_0 from Dengue outbreaks of Londrina, and Sao Paulo in Brazil. Based on the simulations that matched the recorded data, the authors concluded that it is possible to have a self-limiting outbreak if $R_0 < 1$ but the vector–human component is greater than 1. Bowman *et al*. (2005) have used similar mathematical modelling and analysis to assess two main anti-West Nile Virus (WNV) preventive strategies, namely: mosquito reduction strategies and personal protection. They proposed a single-season ordinary differential equation model for the transmission dynamics of WNV in a mosquito–bird–human community, with birds as reservoir hosts and culicine mosquitoes as vectors. The public health implication of this is that WNV can be eradicated from the mosquito–bird cycle (and consequently from human population) if the adopted mosquito reduction strategy (or strategies) can make $R_0 < 1$.

Bisanzio *et al*. (2010) explained the transmission of vector borne diseases like Lyme disease and Tick borne Encephalitis using the 'bipartite networks model'. They concluded that aggregation of vectors on hosts have dramatic consequences on epidemic threshold and predicted that the larger networks are able to sustain the epidemic for longer time.

Modelling the transmission of Ebola viral disease (EVD)

The latest major outbreak of Ebola in Guinea, Sierra Leone, and Liberia in 2014 (Barry, 2014) has renewed interest in

modeling of epidemics. Rachah and Torres (2015) defined a simple Susceptible Infectious-Recovered (SIR) mathematical model that describe the 2014 Ebola outbreak in Liberia and validated the same with numerical simulations and available data provided by the World Health Organization. The authors developed a new mathematical model including vaccination of individuals in order to predict the effect of vaccination on the infected individuals over time.

Meltzer *et al*. (2014), used mathematical modeling to estimate and predict number of cases in Ebola outbreaks in Liberia and Sierra Leone. Future predictions based on present available outbreak data helped in estimating the probable scale of outbreak and enabled public health authorities to be prepared for containment and control.

Siettos *et al*. (2015), developed an agent-based model to investigate the epidemic dynamics of Ebola virus disease (EVD) in Liberia and Sierra Leone, 2014. The dynamics of the agent-based simulator evolved on small-world transmission networks of sizes equal to the population of each country, with adjustable densities to account for the effects of public health intervention policies and took into account human behavioral responses to the evolving epidemic.

In a different study, Lewnard *et al*. (2014) developed a transmission model of Ebola virus that was fitted to reported EVD cases and deaths in Montserrado County, Liberia. They used this model to assess the effectiveness of expanding EVD treatment centres, increasing case ascertainment, and allocating protective kits for controlling the outbreak in Montserrado. The estimated value of basic reproductive number for EVD in Montserrado was 2.49 (95% CI 2.38–2.60), and predictions indicated that existing facilities were inadequate to cope with future cases. Their study also revealed importance of protective kits in containing the number of cases. As a public health outcome, these findings prompted authorities to upgrade the facilities.

Modelling Sexually transmitted diseases (STDs)

Mathematical modeling has also been used to describe transmission of sexually transmitted diseases as HIV/AIDS, syphilis, gonorrhoea, etc (Chin *et al*., 1991; Garnett, 1999; 2002; Garnett *et al*., 1997;2000; 80–84). In case of STDs mathematical modelling can describe the

positions of individuals within the network of sexual partnerships allowing identification of risks for acquiring the disease. Since the transmission mechanism for all these diseases are varied considering human behavior and social dynamics, different mathematical modelling was used for the different diseases. For same disease different mathematical approaches have also been described in studies from different countries (Brunham *et al*., 1990; Morris *et al*., 1997; Rapatski *et al*., 2006). A simple model for HIV/AIDS epidemic was described theoretically by Garnett *et al*. (2002), taking into account various parameters for modelling STDs. Considerable work has been carried out on the mathematical analyses of spread of HIV/AIDS (Brunham *et al*., 1990; Morris *et al*., 1997; Rapatski *et al*., 2006), reports on epidemics from India are rare (Rao, 2003). Rao (2003) described different models to explain the transmission patterns of AIDS in India and highlighted that the variable incubation period in patients contribute to complexity in the modelling of AIDS epidemic. Varied social behavior and interaction patterns in human populations across the globe makes it difficult to construct generalized models for STDs.

Advantages and limitations in disease modelling

Study on transmission dynamics of any disease depends on the nature of data and designing of a model that best describes the outbreak scenario. Fitting of epidemiological data helps in optimizing model parameters especially those which cannot be determined by experimentation. For example, the asymptomatic parameters (whether asymptomatics are capable of transmission, how much and for how long, etc) for influenza in humans cannot be estimated by experimentation or observations but can be estimated from modelling studies provided that total number of asymptomatic individuals are known (by serosurvey) for a particular outbreak (Shil, *et al*. 2011). Modelling and simulation studies based on epidemiological data can also help estimate the effectiveness of control measures, and can be employed for evaluation of vaccine efficacy. However, in spite of advantages modelling of epidemics also has limitations.

Limitations in disease modelling results from improper recording of data especially if it involves contact tracing (methods and efficiency may vary country-wise), and /or assumptions for description of the outbreak scenario. This

is true for air-borne diseases. A major limitation of modelling vector borne viral diseases by employing the Ronald Ross model is estimation of the vector data. In any outbreak scenario, estimating the vector population parameters would require detailed survey and sampling of insects (for arboviral diseases) in the affected area and detection of infection in insects using advanced laboratory based techniques, which may not be possible for local medical or municipal authorities.

SUMMARY AND CONCLUSIONS

The review highlights mathematical modeling as an extremely useful tool for study of the transmission dynamics of a wide range of viral diseases such as Influenza, Ebola, SARS, Dengue, WNV, TBE, AIDS, etc. Modeling studies have provided valuable information related to the spread of epidemics and identification of novel interventions for controlling outbreaks. Besides, the models have proved useful in assessing the potential of preventive measures such as mass vaccination, effects of quarantine and hospitalization in controlling the epidemics. However, mathematical models are not always free from approximations because of non-availability of values of some parameters arising from limitations of primary data collection or some proposed parameter/ factor which cannot be estimated clinically or experimentally. On the other hand, mathematical models, if designed carefully and used for data fitting or simulations, will prove extremely useful as compared to clinical/experimental data, particularly, in epidemic situations. Hence, mathematical modelling has an enormous potential in the study of viral epidemics and framing strategies for containing global pandemics. Effective dialogues and coordination between mathematicians, biologists, epidemiologists and clinicians will pave the way with promising collaborations.

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