Chapter 8

# Unearthing the Complexities of Mathematical Modeling of Infectious Disease Transmission Dynamics

Sutapa Biswas Majee and Gopa Roy Biswas

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/57387

## 1. Introduction

Epidemiology is considered as the study of causes of occurrence and transmission of diseases in human population. It deals with the properties of epidemics in the equilibrium or long-time steady state. It involves prediction and monitoring of the spread of both naturally occurring infection and infection caused by bioterrorism, within a population based on the data regarding course of infection in a single isolated individual. It enables identification of measures for improving the health of the community as a whole. Epidemics can pass through the population at an extremely fast rate, may persist for a long time at low levels, may show cyclic patterns or there may be sudden flare-ups. Therefore, meaningful data collection and data interpretation are the essential components of epidemiology. These data can be exploited to identify trends, make general predictions and assess shortcomings of those predictions. Such prediction can be highly erroneous unless derived mathematically and here lies the utility of mathematical modeling. Moreover, age, clinical status and socio-economic status of the patient, environmental condition, demographic data, meta-population structure, geographical location etc are of great relevance to the disease occurrence, prevalence, persistence and ultimately eradication from a heterogeneous population.

For an in-depth and complete understanding of the unpredictable behavior and pattern of transmission of infectious diseases, both in time and space, epidemiological modeling proves to be a very powerful tool. It enables the epidemiologist to think rigorously and frame policies for protection and treatment of the unaffected and affected population respectively from the invasion by the pathogen. The use of mathematical model in the study of infectious diseases is being envisaged as an insightful alternative to ethically challenging, expensive and at times, practically impossible in vivo and in vitro detailed experimentation and subsequent complicated interpretation. There are instances when the models and the experimental data exist in

a symbiotic relationship and improve our quantitative understanding of the infection dynamics. These models are used to hypothetically disrupt or neutralize genes and simulate infections within a few seconds. Latent infections that can be maintained for decades in a host can be mathematically reactivated to determine the effect on an outbreak. Sometimes, the concept of modeling has been enriched by introduction of an idea from a related field of science as in the case of HIV quasi-species model inspired by molecular quasi-species model in chemistry [1].

Interpretation of variables associated with mathematical modeling helps in estimation of parameters of biological significance and deduction of concepts not directly perceptible from the data. These concepts prove invaluable in giving rise to the observed patterns as also unearthing the complexities underlying the infection. Concept-building, as derived from the framework of mathematical model, gives lead-time to the medical fraternity and the government policy-makers in designing and implementing timely intervention measures for prevention and control of spread of a communicable disease.

Daniel Bernoulli is regarded as the father of epidemiological modeling since he investigated the influence of variolation on life expectancy as early as 1760. One of the fundamental principles of epidemiology, the threshold theorem was established by Kermack and McKendrick in 1927 to establish the dynamics of bubonic plague. Disease persistence in large host population was determined by Barlett.

## 2. Basis of infectious disease

Spread of an infectious disease depends on several factors like factors related to the pathogen, environmental factors, population factors and finally, social structure and behavior of the contagion. Natural birth and death rates of the population are independent of the pathogen. The rate of transmission may differ in different age groups where incubation period may vary. Type and mode of contact or incidence function and immunity duration are known to govern the spread. Geographical location and seasonality are other factors affecting the spread of an infection [2-4].

Complete understanding of infectious diseases requires knowledge of the various processes involved in host-parasite interactions. The two most important processes in these interactions are the epidemiological process associated with disease transmission within the population and immunological process involved in the disease dynamics within the host. Modeling of host-pathogen interactions helps in identification of key factors that may have a major impact on the outcome of an infection. In dynamic models of viral diseases, epidemiological modeling is based on the interaction between the susceptible and infected classes of the population and within-host dynamics is usually overlooked [5]. In any viral or bacterial infection, one of the key determinants of the disease progression within the host is the immunological status which is governed by dynamic interaction between different groups of cells and various signaling molecules [1].

Some of the terminologies associated with infectious disease are (a) infectivity or secondary attack rate, which is defined as the ratio of number infected and number exposed, (b) patho-

http://dx.doi.org/10.5772/57387

genicity or illness rate, which is expressed as the ratio of number with symptoms and number infected and lastly, (c) virulence which may be written as the ratio of number of severe/fatal cases and total number of cases. For example, chicken pox and measles are characterized by high infectivity, high pathogenicity and low virulence whereas, smallpox is recognized by high levels of all the three variables and tuberculosis is found to possess low infectivity, low pathogenicity and high degree of virulence.

## 3. Categories of infectious diseases

The etiological agents of micro-parasitic infections are viruses, bacteria, protozoa or prions, all of which are usually unicellular and of microscopic size and can reproduce very fast. High degree of prevalence of this class of infections among the children worldwide is a matter of great concern to the parents, school authorities and the government. They include measles, rubella, chickenpox, mumps, whooping cough etc. Usual route of transmission is by direct contact through air-borne droplets. These diseases are characterized by high infectivity, short disease generation length and low mean age at infection, on one hand and lifelong acquired immunity following recovery on the other hand.

Macroparasitic infections, caused by parasites, visible to the naked eye (e.g. helminthes, arthropods) are characterized by short duration of immunity following recovery. The number of parasites per host is a critical factor in epidemiology of this category of infections [6].

Microparasitic or macroparasitic infections can occur by either direct or indirect transmission. Usually microparasitic infections are transmitted by direct contact between two individuals as in the case of influenza, HIV, measles etc. The pathogen cannot survive outside the host body. Macroparasites, on the other hand, are indirectly transmitted and they spend a part of their lifecycle outside the host system, freely in the environment. There is a third category of diseases or vector-borne diseases where the causative organism is passed from primary host to the vector and from vector to another primary host as found in case of malaria, filariasis, sleeping sickness etc. [7].

Variation in the characteristics of the infectious agent is manifested as difference in traits and thus arises the need of different dynamics.

## 4. Mathematical model

Mathematical models help in generating and clarifying hypotheses, assessing quantitative conjectures, finding answers to specific questions, determining sensitivities to changes in parameter values and estimating parameters from data in absence and presence of preventive and therapeutic interventions. Therefore, according to input-output approach, mathematical model may be viewed as a system where the facts about the disease serve as the inputs and prediction about the number of infected and uninfected people over time is regarded as the

output. A model is usually expressed in terms of variables which are related to experimentally measurable quantities.

A mathematical model helps in establishment of links between sets of epidemiological data through well-understood mathematical relationships. This is facilitated only through a thorough understanding of various factors associated with the disease like, incubation, transmission and mortality and also factors associated with the vector. Models may also help to characterize and integrate the cellular network and molecular data operating within the different compartments of the host immunity system for disease progression. At a mechanistic level, they help in finding answers to several biological questions which cannot be addressed experimentally. Different conceptual qualitative results and threshold values of paramount importance like basic reproduction ratio, contact numbers, replacement numbers and herd immunity, are derived from mathematical models, since the quantity and diversity of available data is limited. Conditions for local and global stability of various equilibria, relationships among these stability conditions and endemicity are also derived from the epidemiological models. Prediction and recommendations for control of an epidemic outbreak are therefore, the most important outcomes of mathematical modeling of a communicable disease and then they are known as decision models. These models facilitate economic evaluation of different courses of action for mitigation of a particular infection and finally help in selection of optimal control measure [8].

Spatio-temporal progression and temporal development of communicable diseases can be explained by compartmental, agent-based or contact network-based model. In the compartmental model, the host population is divided into different states or compartments, depending on the level of infection in them. Rates of transfer e.g. transmission rate, removal rate between compartments are expressed as derivatives of the sizes of the compartments with respect to time and are assumed to be constant. Ordinary differential equations form the basic framework of compartmental models. In agent-based model, the region of interaction of people in a population is considered as a system of software agents interacting in time and space. It is a high fidelity model and involves complex parameterization and extensive computation. Modern concepts of network theory are employed in dissecting the transmission dynamics within heterogeneous population in a contact network model. Social networking among the individuals influence the possibility, extent and speed of epidemic spreading. This model is intermediate between compartmental model and agent-based model. In this model, the pathogen and the social network within the population are closely intertwined and represented by a node for each individual. The framework of contact network highly depends on the mode of transmission of the disease [2], [9].

Accuracy, transparency and flexibility are the key elements which should be balanced to develop a mathematical model of high quality. For development of any type of mathematical model, mathematical modelers formulate a set of equations by feeding into them various type of factors like the length of time one is ill, the length of time one can infect others, the level of contagiousness of the disease, the number of uninfected individuals who can contract the disease, human behavior and any such known component of disease dynamics. Once a model with biological significance and relevance has been formulated, the model can be fitted to the

http://dx.doi.org/10.5772/57387

experimental data to obtain estimates for the kinetic parameters associated with the system, which are otherwise difficult to obtain experimentally.

Qualitative fitting of the data enables deeper understanding of the disease dynamics and quantitative fitting helps in designing and implementing control measures [7]. Apart from constructing a set of equations, data fitting and estimation of parameters, mathematical model also uses some graphical tools for characterization of dynamical systems. Phase plane technique like, linearization approximation is a graphical tool used to analyze the system dynamics of one state variable as a function of another state variable. In such plot, time dimension is not present but the trajectory of the dynamics is shown by arrows. The second technique is bifurcation diagram reserved for visualization of relatively complex dynamics. Bifurcation diagram is a summary of the asymptomatic dynamics of a dynamical system as a function of a bifurcation parameter [6].

## 5. Compartmental mathematical models

These models can be either Susceptible-Infectious-Recovered (SIR), Susceptible-Infectious-Recovered-Susceptible (SIRS), Susceptible-Exposed-Infectious-Recovered (SEIR), Susceptible-Infected (SI) or Susceptible-Infectious-Susceptible (SIS). Number of compartments in the model depend on the disease being studied and the objective of the study. In this approach, the progress of the disease is defined in terms of level of pathogen within the host.

### 5.1. SIR model

Number or density of individuals in each stage of infection is more important than the load of the pathogen per person in modeling of microparasitic infections. In the SIR model in order to emulate epidemics, population is classified as Susceptible, currently Infectious and Recovered. The total size of the host population is the summation of the three classes. When an individual is concerned, he is assumed to exist in either of the three states. Susceptible means that the individual has never had the disease and is susceptible to contraction of the disease by an infected individual, at random from the population. The mode of transmission of infection depends on the type of the pathogen. Depending on the relative magnitude of the latent period of the infection, the infected host can infect others and then it becomes Infectious. The total time spent in the infected state by an individual is a geometric random variable. When the infectious agent is removed from the system of the infected class or death occurs, they become Recovered with immunity and will never be infected again. In case of a dead individual, he cannot get infected or cannot infect anybody and thus is equivalent to a recovered individual with acquired immunity. Then, it can be assumed that the number of infected individuals tends to decrease towards zero and finally disappears from the network permanently. In the study of disease dynamics, six distinct and well-defined events can be assumed to occur : birth, death of a susceptible individual, death of an infected individual, death of a recovered individual, infection and recovery. Epidemic data supports the assumption that the per capita rate at which a given susceptible individual becomes infected is proportional to the prevalence of infection

in the population. Therefore, according to SIR model, number of cases increases exponentially initially till there has been a sufficient decrease in the proportion of susceptible when the growth rate slows; this process goes on until the epidemic can no longer be maintained and the number of cases goes below a threshold level resulting in disease eradication. Human behavior can affect the disease dynamics in an individual as also in the whole population because it may influence the disease state of an individual, rate of infection or recovery rate and the contact network structure. Therefore, behavioral responses should be considered as an integral part of the study of dynamics of infectious diseases. An intriguing feature of childhood microparasitic infections is that the children are born in the susceptible category as there is no vertical transmission. Birth rate and vaccination affect the recruitment to the susceptible compartment. Moreover, in case of common cold, there is no permanent removal state because the individual enters the susceptible class soon after recovery. This widely used model is applicable for diseases which are contracted by an individual only once in its lifetime and either acquired lifelong immunity develops or death occurs as in case of measles, mumps, SARS, influenza. An important drawback of the model is that it ignores the random effects, specially at early stages of infection, when the number of both susceptible and infected classes is low. This model is unable to describe the spatial aspects of the spread of the disease. Moreover, in this modeling approach it is assumed that each individual has the same amount of contacts as every other individual. Therefore, if the rate of contact varies during course of infection, it cannot be appropriately included in the simple SIR model. Precision in prediction can be improved by incorporating realistic contact patterns or by using modeling approaches possessing higher fidelity.

The SIR model can also be expressed by a stochastic version where the future course of the infection is independent of the past, if present is known completely [2], [6], [9-10].

### 5.2. SIRS

This model assumes that after recovery, the person becomes susceptible again as immunity wanes, i.e. recovered individuals possess short-term immunity [4], [14].

### 5.3. SEIR

It is an extended SIR model where a new compartment or state is added. It is known as Exposed or E which is positioned between the susceptible and infectious compartments. The Exposed individual is infected but not infectious, i.e. the disease remains in latent state [15].This concept can also be explained on the basis of the level of pathogen within the host and immunological status of the host. When the host is susceptible, it indicates that no pathogen is present and only a low level of non-specific immunity exists within the host. As soon as the susceptible encounters an infectious individual, he becomes infected. The pathogen increases in number and the infected host may not show any signs of infection and thus he enters the Exposed compartment. As soon as the pathogen burden is sufficiently high, the Exposed host becomes Infectious and disease is transmitted to another susceptible individual. When the Infectious individual can no longer transmit infection as the pathogen is cleared from his immunity system, he belongs to the Recovered category. The class distinction between Exposed-

http://dx.doi.org/10.5772/57387

Infectious and Infectious-Recovered is not very distinct because of variability in responses between different individuals and variability in pathogen levels over the infectious period [7].

### 5.4. SI model

This modeling approach is unrealistic in case of animal or human infections because here it is assumed that an infected individual remains in this state forever. Hence, the ultimate consequence of the presence of one infected individual in the population is the infection of the entire population. In the early stages of an infection, when the count of infected cases is low, the SI and SIR models behave in a similar fashion as there is limited number of recovered individuals.

### 5.5. SIS model

In this model, individuals run stochastically through the cycle of Susceptible-Infected – Susceptible. Thus, here exist only two states because the infected individual, after recovery, again becomes susceptible to infection. Removal due to death or acquired immunization is not considered. Therefore, the number of infected individuals increases up to a stationary non-zero constant value as observed in case of sexually transmitted diseases [10]. The renewed susceptibility of an individual is due to vast antigenic variation associated with gonorrhea and other similar sexually transmitted diseases [7]. This model is based on assumptions like, different contagion probabilities between different pairs of people, probabilistic recovery from the disease and multiple stages of infection, with varying disease properties [9].

## 6. Deterministic and Stochastic approach to mathematical modeling

If the objective of the study is to model disease propagation in a large population, with continuous variations of population sizes, deterministic model is the most appropriate one. Such model indicates same output or same fate of individuals subjected to same possible events with identical probabilities [6]. For a given set of parameter values, the deterministic model has one solution which can be fitted to data using various methods. The most common method minimizes the sum of squares of differences between observed data and model prediction.

Natural and biological discrete events of random occurrence in a small population cannot be explained by deterministic and continuous modeling and here comes the utility of stochastic modeling. Stochastic models capture the randomness of birth and death rates associated with disease dynamics and also the variability among disease strains. The earliest stages of an infection are stochastic. This occurs because encounter with a pathogen may either lead to an infection or elimination from the system. Stochasticity decreases as the number of cases increases. Emergent behaviors that have neither been defined nor expected are simulated in this modeling approach. Probability distributions associated with such systems are typically memory-less. If the objective of modeling of disease dynamics is to establish the conditions for disease eradication, or if irregular epidemics are to be modeled, stochastic model is the choice. Stochasticity can induce chance extinctions of the disease and it introduces variances and co-

variances that can influence the deterministic behavior. Stochastic simulations are computationally intensive.

In stochastic modeling of HIV dynamics, it is assumed that the viral population is governed by the availability of target cells that can be infected and does not take into account the contribution of the immune responses in the control of virus load.

Stochastic extinction or disease eradication by chance occurs when an infected individual fails to reproduce and transmit the infection and ultimately the pathogen dies out.

An interesting thing to note at this juncture is that deterministic model can be transformed to the corresponding stochastic model by conversion of deterministic rates into the probabilistic ones on the basis of a fixed reference volume of the model. This has been done in the analysis of dynamics of HIV and the opportunistic co-infection TB by incorporation of the response of cytotoxic T-lymphocytes in absence and presence of HAART therapy by altering the model's parameters. Evolution of drug resistant strains can also be assumed to exhibit a stochastic pattern.

A combination of deterministic and stochastic approaches will be the most effective one because of their complementary features, although it may be time-consuming and may exploit more resources [1], [7], 12, [16-18].

As no element of chance or uncertainty is involved in the development of deterministic models, they account for the mean trend of a process only. However in addition to the above feature, stochastic model also accounts for the variance component around the process. Initial epidemic growth of an infection cannot be properly approximated by deterministic SIR model. This occurs because at this stage only a seed of infection is introduced in contrast to the large population at later stages. Probability that an infection will occur is governed by demographic stochasticity. In case of stochastic models, some parameters are characterized by a probability distribution, instead of a fixed constant value, as observed with the deterministic models [6]. Given a stochastic transmission model, most inferential methods rely on likelihood. Given a likelihood, inference can proceed along conventional lines, using tools such as maximum likelihood estimation, expectation maximization algorithm, rejection sampling and Markov chain Monte Carlo methods.

## 7. Insights into conceptual results from mathematical model

Two approaches can be used to determine the time-scale of disease transmission by utilizing data on individual-to-individual chains of transmission. Estimation of disease generation time (T) is one approach. It may be defined as the expected length of time between infection of an index case and infection of his or her secondary cases. It is the duration of latency plus infectiousness. The generation time of measles is approximately 14 days. A short generation time indicates rapid transmission whereas a longer T suggests slower spread but longer carriage. The duration of carriage of pathogens represents an upper limit on T and it can be concluded that directly transmitted acute infections have $T < 1$ month and chronic infections

http://dx.doi.org/10.5772/57387

have T values in the order of months or years [19]. But, determination of generation time becomes complicated if the disease possesses asymptomatic periods of infection of variable or unknown duration. Another quantity that is estimated is the serial interval. It is the time between clinical onset of symptoms in the index case and the clinical onset of symptoms in the average secondary case [2].

In a system of differential equations, an equilibrium point is a point at which all the equations equal zero. This indicates that the state of the system is not changing. In a mathematical model, a disease-free equilibrium (DFE) and one or more endemic equilibria are present. The DFE indicates that the entire population is susceptible since not a single infective exists in the population. Endemic equilibrium is steady-state equilibrium produced by spread of infection. If the solutions of the equations near the equilibrium points tend toward the points with time, they are said to be locally stable. An equilibrium point is referred to as globally asymptotically stable if the behavior of the system at any point tends toward the equilibrium point as time tends toward infinity.

The stability of DFE and existence of other nontrivial equilibria can be determined from a ratio, known as basic reproduction ratio [20]. A very brief description of the essential conceptual results from mathematical modeling has been given in Table 1.

| Parameters | Description |
|---|---|
| Disease generation time | Time from the moment one person becomes infected until that person infects another person |
| Equilibrium point | Can be categorized as a. disease-free equilibrium point when there is no infection in either the host or the vector or there is no pathogen and b. endemic equilibrium where the disease persists in the population. Both are steady state solutions. |
| Basic reproduction number | Number of secondary cases caused by one primary case introduced into a population that is wholly susceptible |

**Table 1.** Glossary of important parameters associated with mathematical modeling of infectious diseases

## 8. Basic reproduction ratio

A key concept or parameter in epidemiology, the basic reproduction ratio, $R_0$ is being extensively studied during deterministic, non-spatial, unstructured modeling of in-host population dynamics of microparasitic infectious diseases, once they have been established. It is defined as the expected number of secondary individuals infected by an individual during his or her entire tenure of infectious period. Its derivation is applicable even when non-constant transmission probabilities between classes (i.e., non-exponential lifetime distributions) are assumed. If its value is greater than 1, the infection spreads across a non-zero fraction of

susceptible population. If the spreading rate is too low and $R_0$ cannot cross beyond the threshold level, it is not feasible to affect a finite proportion of population and disease dies out in a finite time. In a contact network model, the disease cannot replenish itself and ultimately dies out after a finite number of waves, if $R_0 < 1$ with probability 1. Disease persists with positive probability, at least by infecting one person in each wave, if $R_0 > 1$. Keeping and maintaining the value of $R_0 < 1$ reflects the stability of the disease-free equilibrium and creates a condition for clearing of pathogen from the population and thus it is the goal of any public health initiative designed for containment or control of infection. Moreover, the estimation of $R_0$ plays a crucial role in understanding the outbreak and potential danger from emerging infectious disease. The concept of $R_0$ has also been developed for complex models like stochastic and finite systems, models with spatial structure and also macroparasite infections. Comparison of $R_0$ values, based either on their numerical values or area under the infectiousness curve, helps in estimation of relative intrinsic transmissibility of the pathogens [9], [10], [21], [22].

There are also alternative approaches of estimating $R_0$ from available incidence or epidemiological data which require simplifying assumptions for numerical estimation of some unknown parameters. It is assumed that the host population is homogeneous, mixes uniformly and is of constant size in a constant state. The number of contacts per infective is independent of the number of infectives. Infectivity and mortality do not depend on age, genetic make-up, geography. Moreover, it is assumed that all individuals are born susceptible and as soon as disease is acquired, they are no longer considered susceptible. Spreading pattern of the epidemics is controlled by the generation time-scale. All these assumptions may never be fully realized in a practical clinical setting. $R_0$ can be expressed as the ratio of the life expectancy and mean age of acquiring the infection. Thus, higher the $R_0$, lower is the mean age at infection. Another important relationship that can be derived is that the mean age at infection is the reciprocal of the force of infection. A key parameter, the coefficient of transmission for airborne diseases, can be determined from the value of the force of infection. Alternatively, $R_0$ can be estimated from the intrinsic growth rate of the infected class, which is highly dependent on collecting accurate data. Stochastic fluctuations can affect the value of growth rate. In case of vector-borne disease like dengue, $R_0$ was calculated from the survival function, assuming spatial compartments of varying vector density. For multiple classes of infectives, $R_0$ can be defined per infection cycle [6], [10], [21].

From sensitivity analysis, it has been found that different infection-and population-related factors may affect $R_0$ like, transmission rate, vector mortality, incubation period of the vector, the relative infectiousness after isolation [21].

For both measles and whooping cough in England and Wales from 1945 to 1965, $R_0$ has been found to be nearly 17. For the H1N1 epidemic in UK, $R_0$ has been estimated to be 1.4. Estimation of $R_0$ for SARS by different groups have mostly given the values in the range of 2-4, although a wide range of 1-7 has also been found in the literature. For smallpox, the $R_0$ was found to be in the range of $4 < R_0 < 10$. Though an upper bound has been found for pandemic influenza, no lower bound could be obtained. For AIDS, $R_0$ is always greater than 1, especially in African countries and it depends highly on the sexual behavior. For

homosexual population in the United Kingdom, $R_0$ is close to 4 and approximately 11 for female prostitutes in Kenya [7], [13], [22].

### 8.1. Significance of basic reproduction ratio

The magnitude of $R_0$, along with the disease generation time, help in assessing the time scale of infection, implementing sustainable control measures at the most appropriate time and justifying implementation of costly approaches in management of infectious diseases. Low value of $R_0$ for any infection suggests that the epidemic can be controlled, either by adopting single or combined putative containment procedures [21], [22].

Condition for endemicity can be deduced from an idea of $R_0$. Disease is said to exist in an endemic state when it persists in the population at a low and constant level of prevalence, for which there should be a continuous supply of susceptibles. This happens if deaths and births occur at equal constant rates keeping the population turnover rate at a fixed value. An outcome of this assumption is the negative exponential distribution of age. At endemic equilibrium, the relationship between the proportion of susceptible in the population and the basic reproduction ratio is inverse [6].

Though $R_0$ is the widely accepted and used indicator of control measure, it has been observed that different control approaches may produce same degree of reduction of $R_0$ but not same effect on the growth rate. Factors such as timing of secondary infections, negative impact of control measures on the population are not considered while implementing public health initiatives based on the basic reproduction ratio [21].

### 8.2. Alternatives to $R_0$

$R_0$ is a highly pathogen-centered parameter and recently, a host-centered parameter has been evolved, the basic depression ratio, $D_0$. An alternative parameter for heterogeneous population has been developed, type reproduction number, T which indicates the efficacy of the control measure against a particular subtype of host population, from which if infection is eradicated, the disease will not sustain at all [21].

In case of a population which is susceptible after acquiring immunity from a previous epidemic or due to vaccination, instead of $R_0$, $R_{eff}$ or effective value of $R_0$ is used. $R_{eff}$ is a time-dependent quantity that accounts for the population's reduced susceptibility. If $R_{eff}$ is greater than one, the number of infected individuals grows and decreases if $R_{eff}$ is less than one. Therefore, the critical proportion of susceptible is given by $R_{eff}$ equal to one [11]. The parameter can be determined by fitting deterministic epidemiological model employing a generalized least squares estimation scheme [23].

In case of seasonally driven epidemics as with different childhood microparasitic infections, it is necessary to determine the number of susceptible left after a major epidemic ($S_0$). If $S_0$ goes above a critical threshold value, epidemic outbreak may recur in the next year or there will be a skip i.e., a year when epidemic fails to initiate [14].

## 9. Strategies for containment of an infectious disease

Barlett postulated that any infectious disease cannot be maintained if the population size is below the critical community size unless there is supply of susceptible or regular migration of the infected class from the adjoining places. This will ultimately lead to disease extinction. Disease is said to fade-out if the duration of disease extinction is more than the disease generation length [6]. Although, theoretically, it may be possible to estimate and predict the time for disease eradication from the population, practically it is not feasible. Therefore, in practice, attempts are made to prevent spreading of the infection.

Once the epidemiological data have been modeled into a reliable mathematical model, they can be used to identify population subgroups at high risk of disease and develop preventive interventions or measures according to time, place and person. These measures include education, immunization, quarantine regulations or social distancing to restrict interaction with others and treatment options. Mathematical modeling of intervention strategies can be done in two ways. In the first method, the goal is to assess the effect on the disease dynamics by changing the value of a constant parameter associated with the disease. This indicates the best parameter value for a given performance measure. In the second method, intervention measures are varied as a function of time and the objective is to determine the best parameter value for a given performance measure. Pontryagin's Maximum Principle (PMP) is applied for comparison of a wide range of time varying functions. The best strategy for mitigation of spreading of a contagious disease would be the one which evolves with time during different phases of infection and thus focuses on progressively changing classes of populations. Optimal control theory suggests the most effective mitigation strategy to minimize the risk of individuals being infected by applying and balancing vaccination and administering drug in a cost-effective manner. Based on this, vaccination has been found to be the most common strategy in reversing the epidemic growth of an infection within the population in the initial stages of an outbreak. But in absence of the strategy, due to some reason or other, medical practitioners either isolate symptomatic individuals or trace and quarantine contacts of symptomatic cases. These strategies require proper diagnosis of the symptoms of the disease in each and every individual. Efficacy of any implementation strategy is decided by the efficacy at which the infected person is isolated and the efficacy at which the persons with whom the infectious person came in contact can be quarantined. An infection can be sufficiently controlled if the values of basic reproduction ratio and the proportion of transmission occurring asymptotically can be reduced below a critical line. Since SARS is characterized by low $R_0$ and low infectiousness prior to clinical symptoms, effective isolation of symptomatic patients can sufficiently control an epidemic outbreak. For those diseases where the proportion of asymptomatic transmission is more than $1/R_0$, contact tracing should be added to the set of control measures used. This proportion can be determined from the longitudinal data on clinical symptoms and pathogen load within the patient. Mathematically, it has been deduced that influenza is more difficult to control than small pox. Moreover, quarantining and contact tracing would not provide any extra benefit in case of influenza because of very short incubation and infectious periods. AIDS has taken an alarming proportion because of high risk of pre-symptomatic transmission and under such circumstance, self-isolation and contact tracing would provide little respite [10], [22], [24], [25].

http://dx.doi.org/10.5772/57387

## 10. Vaccination

Implementation of proper and effective vaccination protocol is of primary concern to the epidemiologists and public health decision makers. Vaccination program is usually a government initiative applied on large spatial and temporal scales to reduce the level of complexity of disease. The ultimate goal of any vaccination program is to keep the value of basic reproduction ratio below unity by altering the various control parameters. Mathematical modeling of vaccination recognizes that linear transfer occurs between the susceptible and the removed compartments. For modeling purpose, important variables related to vaccination that should be included are vaccination rate, i.e. the rate at which the susceptible individuals are vaccinated and efficacy or the proportion of susceptible left unprotected even, after immunization [26].

Two schemes are being widely employed worldwide for prevention and eradication of vaccine-preventable infections-mass vaccination and pulse vaccination. Mass vaccination is usually carried out in infants before the mean age at infection. But, it may not always be practically the most effective approach for global disease eradication. Pulse vaccination, on the other hand, is a cheaper and a better alternative where periodic vaccination of a certain proportion of the population renders sufficient and enough protection against further spread of the disease as the percentage of susceptible is always maintained below the threshold level required for an epidemic to start. But, pulse vaccination suffers from the side effect of resonance. Impact of single- and multiple-dose vaccination on rubella eradication has been studied extensively in an age-structured model with constant transmission rate using Floquet analysis. It has been established that eradication likelihood is governed by the effective duration of immunity. Booster vaccination has also been studied, but, in less details. Permanent immunity is conferred by booster dose in contrast to partial immunity imparted by primary vaccines. A new threshold quantity, known as re-infection threshold in case of vaccination-induced partial immunity, indicates the condition when vaccination will not succeed thereby producing high levels of infection. Prevention or reduction in epidemicity is more readily achievable by booster vaccination, depending on the level of primary vaccination program, because it has the capacity to increase the vaccination coverage and herd immunity of the population as a whole. Outcome of a booster dose depends highly on precise timing of the additional vaccine doses as well as the proportion of individuals receiving the second-dose. During vaccination, decision of the individual or mass to undergo program greatly affects the efficacy of the program. Therefore, human behavior plays a significant role in ensuring success of the strategy [3], [6], [27].

An interesting thing to note while conducting mass scale immunization is that it is possible to protect the whole population from an outbreak even if there are some susceptibles in the population, at less than 100% immunization. This effect is called herd immunity. When $R_0 < 1$, the DFE is globally asymptotically stable resulting in disease eradication as observed in case of measles. Vaccination reduces the force of infection and increases the mean age at infection when the infection may be acquired. Vaccination desynchronizes local dynamics which will prevent migration of susceptible population from neighboring places and thus can facilitate extinction of the disease. However, vaccination of each and every individual in the susceptible

class is practically not feasible and more so, in economically backward countries. Therefore, the critical fraction or proportion of population that needs to be vaccinated is to be determined. Moreover, desired degree of success may not be always obtained due to vaccination because of less than optimum coverage, irregularities in the supply of vaccines, use of low-efficiency vaccines or waning rate of vaccines. All these may lead to re-emergence of disease outbreak, sometimes with increased intensity, owing to the resurgence of the susceptible class finally resulting in serious side effects.

Vaccination coverage depends on the characteristics of the endemic equilibrium. At equilibrium, the replacement number, R is equal to the product of basic reproduction ratio and the proportion of susceptibles i.e. $R=R_0s^*$. The replacement number is defined as the average number of secondary infections produced by a typical infective during its entire course of infectiousness. Vaccination coverage of $p$ reduces the proportion of susceptible to 1-$p$. Higher the magnitude of $R_0$, higher is the vaccination coverage and is complicated by parameter such as vaccine efficacy. Therefore, for disease eradication to occur, $R=R_0s^*(1-p) < 1$ or $p > 1-1/ R_0$. The critical vaccination coverage is expressed by the formula, $p_c=1-1/ R_0$ and the value has been found to be 0.94 and 0.86 respectively for measles and rubella. An increase in the value results in a decrease of the spatial synchrony of disease dynamics. Smallpox has been successfully removed from the face of the earth because it possesses the least critical vaccination coverage. Vaccine efficacy of 0.97 represents that 3% of those vaccinated do not become immune.

Optimal vaccination coverage and frequency of pulse vaccination has been studied with the help of Pythagore theorem [6]. The important terminologies associated with vaccination has been presented in Table 2.

| Parameters | Description |
|---|---|
| Herd immunity | Immunity and protection of the entire community achievable by vaccinating a proportion of the population and creating immune individuals |
| Basic reproduction number under vaccination | Number of secondary cases caused by one primary case introduced into a population in which a proportion has been vaccinated |
| Critical vaccination proportion | Proportion of population to be vaccinated to achieve eradication by maintaining Basic reproduction number under vaccination equal to one |
| Vaccine efficacy | Effectiveness of the vaccine to induce immunity |
| Eradication likelihood | Determined by effective period of immunity |
| Re-infection threshold | Occurs during transmission induced by partial immunity. It is a threshold quantity above which levels of infection will be high and vaccination fails |

**Table 2.** Glossary of important parameters related to vaccination

http://dx.doi.org/10.5772/57387

## 11. Quarantine

Quarantine refers to intentional or forceful isolation of individuals suffering from diseases like leprosy, plague, cholera, typhus, yellow fever, smallpox, diphtheria, tuberculosis etc. The ultimate objective of the process is to reduce the average infectious period by isolating some infectives, so that they do not transmit the infection. To study the effect of quarantine, a new class Q of quarantined individuals has been included in standard SIS and SIR endemic models. They include those who have been removed and isolated either voluntarily or coercively from the Infectious class. The quarantine reproduction number, $R_0$ depends on the quarantine rate constant which governs the transfer rate out of the Infectious class into the Quarantine class [28].

## 12. Evolution of mathematical modeling

Epidemiological modeling has undergone numerous revisions and improvements to cope up with emerging new infections and discovery of new concepts and basis of existing infections. It is well-known that increase in model complexity by including more relevant biological details improves the accuracy. But it is practically not feasible to construct a fully accurate model. There will always be some factors related to host, pathogen, environment or population which cannot be estimated or predicted. Processes of random occurrence affect the degree of accuracy of model. Predictability of the model depends highly on a strong interplay between statistics and models for estimation of parameters from epidemiological data.

The key assumption of deterministic mathematical model is the existence of homogeneous and constant population, where it is assumed that, the death of a susceptible, infectious or recovered individual is immediately compensated by the birth of a new susceptible. In actual practice, heterogeneity is observed where the population can be divided into several homogeneous subpopulations or groups on the basis of mode of transmission, contact patterns, latent period, infectious period, genetic susceptibility or resistance as well as socio-economic, cultural, demographic and geographic factors. All these complexities can be suitably incorporated in a multi-group model and can prove effective in explaining the dynamics of sexually transmitted diseases such as gonorrhea or AIDS [29]. Population-level heterogeneities that, if included can improve the model's accuracy and predictive ability, include age, gender, behavior, genetic susceptibility [7]. Influenza infection is well-studied and well-modeled. But, there are still several aspects of the infection which have not been included in model construction like, the contribution of strain-specific cell tropism, pre-existing immunity, effect of host genetic factors on virulence and transmissibility of a particular strain. The model may be modified to determine the severity, duration and outcome of infection progression within an individual [30]. Moreover, drug resistance may develop. Therefore, a model with an immune response can be generated for better insight into the disease dynamics and the predictions from the model are different from those of a model formulated without an immune response. Two-phase solution can be used to study different viral infections. Study of models, specific for

influenza or H1N1 require careful parameterization to match available data and it should reflect both statistical uncertainty and uncertainty in data itself [13].

A new rule, known as 20-80 rule has been proposed by researchers for certain infectious diseases which show unique features. According to the rule, 20% of the individuals are responsible for 80% of onward transmission and they are known as super-spreaders. This gives rise to variation in the number of secondary infections per infected individual which is denoted by Z. It is described by two parameters-mean $R_0$ among infections and dispersion parameter, K. A small K (<0.1) indicates that a small proportion of infected individuals actively transmit the pathogens whereas, a large K (>4) indicates that all infected individuals are equally responsible for onward transmission [19].

In multiple-host diseases, different hosts or reservoirs are involved. Dynamics of the disease itself may vary in the different hosts and the mode of transmission from one host to another is quite complex. All these factors should be borne in mind during study of these diseases [6].

In viral disease like Hepatitis B, there is a carrier state where the individual is not fully recovered and is able to transmit low level of infection throughout his life. Some diseases like chlamydial infection is characterized by infected individual who is asymptomatic but is able to transmit disease. Again, meningitis may remain benign for long within population but may exhibit sporadic symptomatic outbreaks [7]. Infectious diseases which are characterized by multi-factorial pathologies or where concurrent infections prevail in immune-compromised hosts usher in complexities in mathematical modeling [1]. A common feature of certain childhood infections is the periodical occurrence of high levels of infection of school-going children which necessitates the inclusion of a time-varying contact rate between susceptible and infected classes of individuals in the model, which is then known as seasonally-forced model and is recognized by a sinusoidal function. The concept of seasonality in the coefficient of transmission and temporal heterogeneity was introduced by Soper to account for the high amplitude outbreaks of measles in Glasgow. These types of diseases are characterized by strong annual, biennial and sometimes irregular oscillations. In India, polio has been found to occur annually. Measles is known to exhibit biennial occurrence for extended periods in London. It has been noticed that the same disease can have different temporal patterns during different epochs which may be attributed to changes in epidemiological factors, e.g. population birth rate, magnitude of disease transmission, and strength of seasonality [14]. Modeling of measles dynamics is best achieved by incorporation of an epidemic oscillator, which takes into account the birth rate variations and can analyze chaotic behavior of epidemic outbreaks. It has been observed that high birth rates drive measles dynamics to annual cycles and diminishing birth rates result in biennial patterns. Vaccination causes irregular cycles. Complex oscillations arise due to interactions between the externally imposed annual seasonality and intrinsic oscillatory dynamics of the infection itself [26]. The approach of "term-time forcing" should also be employed for temporally forced models of another childhood bacterial infection, pertussis or whooping cough. Though both measles and pertussis possess identical values for basic reproduction ratio, yet they exhibit different dynamics because the infectious period in whooping cough is longer than that of measles. School holidays during Christmas

http://dx.doi.org/10.5772/57387

does not affect severely the transmission of the disease [11], [27]. For better understanding of the model with periodic perturbations, bifurcation diagram proves beneficial [7].

Assumptions that have been discussed in a previous section hold true for developing countries where all individuals are exposed to similar death pressure, irrespective of age, due to the environmental conditions and lack of medical facilities. But the situation differs in developed countries where square shape age distribution is manifested. This can be attributed to availability of proper medical care. Modeling becomes somewhat complicated in analysis of macroparasitic infections owing to their inherent differences from the infections caused due to microparasites. In case of microparasitic infections, the internal dynamics of the pathogen within the host is not as crucial as the host's infection status. But, the complex life cycle of the macroparasite within the host necessitates inclusion of this parameter in modeling of macroparasitic infections. Moreover, disease transmission and pathogenicity are highly related to the load of the causative organisms within the host system [6], [7].

Furthermore, complex dynamics may be followed by the infections, where the causative agent can undergo mutation and can create a class of population, susceptible to the new strains. Previous infections in those cases confer only partial cross-immunity and thus, history of infection is important. Number of parameters in the model therefore, increases exponentially with the number of strains. In these circumstances, either reduced transmission approach or polarized immunity concept is applied [11]. Emergence of drug resistant strains is an issue of great concern which should be included in modeling disease dynamics. Sexually transmitted diseases unfold a different picture because of high risk of exposure of sexually active individuals, belonging to a particular age group.

Complexities may also arise in modeling of diseases in presence of an optimal control measure where there is a delay element between implementation of isolation and quarantining. Inclusion of delay increases the proportion of transmission occurring with an asymptomatic or pre-symptomatic infector and hence, necessitating adoption of stringent measure including contact tracing. Oversimplification may fail to estimate the efficacy of contact tracing in reducing the transmission. However, in this delay period, the patient may practice self-isolation depending on the nature and severity of the symptoms and the time scales involved [22].

In a modified SIR model with "skipping" dynamics for diseases like influenza, it has been shown that the immunity of hosts depends on previous exposure to the disease and immune memory. Due to mutational changes in influenza virus or antigenic evolution, hosts may be re-infected with the disease every few years, with years of 'skips' or gaps in between [31].

The simple SIR model has been extended to include the effects of saturation where the incidence rate is not bilinear in S and I but a general function $f$(S,I). It is assumed that in presence of large number of infectives in the population, the number of contacts per time diminishes [3].

The simplistic SIR model has evolved into biphasic SIR model (B-SIR) to explain the key features of multi-ennial epidemic cycle. In this model, the SIR dynamics alternates between a relatively fast epidemic phase in which there is a significant increase in the number of infected as well as a rapid decline in the count of the susceptible and a slow build-up phase

characterized by continuous replenishment of susceptible. This enables estimation of threshold(bifurcation) values at which there will be a switching from biennial to annual epidemic dynamics [14].

A likelihood-based methodology has been developed which assumes the generation interval to follow Weibull distribution and a specific infection network underlies the observed epidemic curve [23].

An agent-based model in the study of tuberculosis has revealed that recruitment of increased number of resting macrophages to the infection site in tuberculosis increases bacterial load. This suggests that the inflammatory response may be detrimental to the host [32].

Since, application of mathematical modeling approach shows that vaccination decreases the mean age at infection, it deduces that implementation of vaccination programs can actually increase the incidences of absolute number of serious cases, if the probability of disease complications increases with age. This is an interesting paradigm of mathematical modeling. In case of imperfect or ineffective vaccination, a backward transfer between the susceptible and recovered compartments must be considered because the vaccinated individuals may come back to the susceptible category or may become directly infected through nonlinear transmission. This behavior gives rise to bi-stability and backward bifurcation [26].

Exponentially growing population and incidences of mortality due to childhood infections in developing countries are not considered in modeling of infections where the host population is assumed to be of constant size. The component of heterogeneity also exists in cases of sexually transmitted diseases. This is further complicated by the fact that, unlike other infections, recovery from STD does not guarantee development of acquired immunity. The currently existing rationale of mathematical modeling may need to be modified while investigating mother-to-child diseases and diseases transmitted by multiple users of syringe as in AIDS [6].

A hierarchical dynamics has been observed in epidemic outbreaks of complex heterogeneous networks. Propagation of infection occurs via a cascade from higher to lower degree classes [10].

In most of the cases, epidemiological processes within the population and immunological processes involved within the individual host are considered separately, with no explicit interaction between the two. Infectious diseases, caused by RNA viruses are characterized by high mutation rate and short generation time of the viruses indicating that evolutionary processes occur rapidly and evolutionary outcomes depend on the fitness of viral mutants at different stages of viral lifecycles and interactions between viral variants. Moreover, ecological and epidemiological factors, such as host contact patterns, transmission routes, host movements also govern the success of viral transmission in a population. In this approach, three different time scales are considered-a fast time scale for within-host dynamics, an intermediate time scale for epidemiological process and a slow time scale for the environmental contamination [5]. Link between the evolutionary process at the pathogen level and the ecological processes at the host population level can be established by phylodynamics [11]. The phylo-

dynamic approach can be successfully utilized in mathematical modeling of such viruses like dengue, human respiratory synctial virus, Hepatitis C, Toxoplasma etc. [19], [33], [34].

Several new modeling concepts are being explored for detailed description of diseases like AIDS, tuberculosis. These include differential infectivity (DI) and staged progression (SP) model [29]. For modeling of infectious diseases with long infectious period and where there are multiple alternative disease progression pathways and branching, or where there is considerable difference in virulence or when only a part of the infected population undergoes a treatment whereas the rest remains untreated, staged progression models seem to be the most suitable [35]. Individuals infected with HIV sequentially pass through a series of stages, being highly infectious in first few weeks after their own infection, then having low infectivity for many years, and finally becoming more infectious as their immune system breaks down and they progress to full-blown AIDS. Investigation of the influence of imperfect vaccine on HIV transmission by individuals in AIDS stage with the help of SP model revealed that the imperfect vaccine can eliminate HIV in a given community at vaccination reproduction number less than unity, but the disease will persist otherwise [36], [37]. Since, tuberculosis is characterized by presence of very long latent period and infectious period, time is not considered to be constant in modeling of the disease. The latent period and infectious period are divided into n-stages and stage progression model with bilinear incidence was formulated [39]. Characteristic features of DI and SP models have been given in a tabular form (Table 3).

| DI model | SP model |
|---|---|
| Suitable for diseases where viral levels differ between individuals as in sexually transmitted diseases and also diseases where infectivity depends on parasite or viral loads in infected hosts or vectors e.g. malaria, dengue fever. | Suitable for modeling of diseases exhibiting variability of infectiousness with time as in AIDS or where time-scale of disease transmission is too long. |
| Infectives are divided into a number of a groups according to their infectivities. Total population size is assumed constant. | Total host population is partitioned into the following compartments: the susceptible compartment, the infectious compartment , whose members are in the *i*-th stage of the disease progression, and the terminal compartment. It is assumed that there is no recovery from the disease, and thus the only exit from the terminal compartment is death. |
| Infection-free equilibrium is globally stable and there exists a unique endemic equilibrium for these models | Disease-free equilibrium and unique endemic equilibrium have also been established with these models |

**Table 3.** Characteristic features of DI and SP model

Healthcare-associated infections (HCAI) or nosocomial infections or hospital acquired infections are source of great concern in developed as well as developing countries. Such infections can be modeled using either deterministic or stochastic approach for evaluation of control policies. This requires sound model parameterization and sensitivity analyses [40].

Influenza control is a challenge since it is difficult to predict the predominant strain that will be circulating each season. Successful vaccination program can be designed from a model which includes the drift process (via the emergence of new strains), the co-circulation of existing strains and pre-existing immunity in the population. A good model is able to reproduce the herald wave phenomenon of strain persistence from one influenza season to the next in temperate regions [41].

Recently, multi-scale models are being developed which will help in predicting virulence, transmissibility, at the population level, susceptibility or resistance to drugs without conducting tough and time-consuming laboratory experiments. For development of these types of models, complete genome sequence of the pathogen should be made available, which will allow mapping from genotype to complex phenotypes.

Numerous modeling approaches contain data estimated from the literature and for such cases extensive sensitivity analysis may prove beneficial. In uni-variate sensitivity analysis, impact of variation of one parameter by a certain percent on the outcome of the model is measured while all other parameters are held constant. Such analysis can be graphically represented on a tornado plot. In multivariate analysis, impact of multiple parameters is studied through Monte Carlo simulations [38]. Other multilevel fitting schemes and Bayesian/Markov chain Monte Carlo frameworks may also be useful [30].

## 13. Conclusions

Infectious diseases pose a great threat to human civilization and world economy. Therefore, constant efforts are being made to prevent their occurrence, recurrence and spread. There are certain infections which do not manifest themselves as definite symptoms in the infected host for a long period of time but can be highly lethal at the end. Research is focused on development of economically viable new intervention strategies for any type of infectious disease with the aid of mathematical modeling. Symbiotic and synergistic relationship should exist between mathematicians and biologists for detailed analysis of the biological processes involved in host-pathogen interactions. Mathematical models involve assumption, abstraction, simplification and description of the most complex system of infectious disease, by the use of language of mathematics. Each element of host and pathogen can be monitored and varied simultaneously without actually performing any experiment to ascertain the role of the element in disease dynamics. Epidemiological modeling enables extrapolation of population behavior from individual behavior and long-term behavior from dynamics of early stage of infection following consideration of different epidemiological factors. Surveillance data, physicians' reports and data acquired from the hospitals are the sources for individual-to-individual chains of transmission. Despite the fact that mass human behavior becomes unpredictable at times, especially during a disaster, concerted rigorous approach adopted during model development can build up a strong framework for future planning. Extensive long-term data and refined mechanistic understanding of evolutionary and transmission dynamics has enriched the field of mathematical modeling and provided insights in shaping the global public

health response to a pandemic. The foremost important contribution of mathematical epidemiology to healthcare professionals is the concept of basic reproduction ratio and epidemic threshold. From a medical or public health perspective, models are instrumental in policy-making, service planning, risk assessment and monitoring performance of infection control programs. Decision of whom, how and when to quarantine, vaccinate and initiate therapy can be planned and implemented successfully from the outcomes of a model of high quality. The source of complexity in models is the occurrence of huge variability in infection profiles, parameter values and time scales. However, complexity ensures model accuracy. Selection of type of model and its degree of complexity depends on the purpose of modeling and questions to be addressed. Failure to understand, forecast and control an epidemic outbreak in a particular locality can indicate that some of the key disease parameters and elements of biological complexity might have been overlooked while developing the model. One underlying reason for this may be traced to a key fundamental feature of mathematical model. Unless the model is tightly fitted to the experimental data, there remains a doubt on the reliability of the parameter estimates obtained from the model. At the end, it can be said that mathematical model helps in integrating several disease-related facts and factors into a cohesive structure, better visualization of a complex system, determining the plausibility of epidemiological explanations, prediction of unexpected interrelationships among empirical observations and prediction of impact of changes in the system.

## Author details

Sutapa Biswas Majee* and Gopa Roy Biswas

*Address all correspondence to: sutapabiswas2001@yahoo.co.in

NSHM College Of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata-Group of of Institutions Kolkata, West Bengal, India

## References

[1] A Sorathiya, A Bracciali and P Liò (2010). Formal reasoning on qualitative models of co-infection of HIV and Tuberculosis and HAART therapy. BMC Bioinformatics 11(doi:10.1186/1471-2105-11-S1-S67).

[2] N B Dimitrov and L A M Dimitrov (2010). Mathematical approaches to infectious disease prediction and control. In Infectious Disease Models Tutorials in Operations Research, INFORMS (ISBN: 978-0-9843378-0-4).

[3] S Funk, M Salathe and V A A Jansen (2010). Modeling the influence of human behavior on the spread of infectious diseases: a review J. R. Soc. Interface 7, 1247–1256.

[4] N Piazza and H Wang (2013). Bifurcation and sensitivity analysis of immunity duration in an epidemic model. Int. J. Numer. Analy. And Modeling Series B Computing and Information 4, 179-202.

[5] Z Feng, J Velasco-Hernandez and B. Tapia-Santos (2013). A mathematical model for coupling within-host and between-host dynamics in an environmentally-driven infectious disease. Math. Biosci. 241, 49-55.

[6] M Choisy, J F Guegan and P Rohani (2007). Mathematical modeling of infectious diseases dynamics in Encyclopedia of infectious diseases: modern methodologies. Edited by M Tibavrenc, John Wiley and Sons, 379-403.

[7] M J Keeling and P Rohani (2007). Modeling infectious diseases in humans and animals. Princeton University Press.

[8] H Squires and P Tappenden (2011). Mathematical modeling and its application to social care. Methods Review 7, 1-22. (ISBN 978-0-85328-452-9).

[9] D Easley and J Kleinberg (2010). Networks, Crowds, and Markets: Reasoning about a Highly Connected World. Cambridge University Press, (http ://www.cs.cornell.edu/home/kleinber/networks-book/).

[10] M Barthelmya, A Barrat, R Pastor-Satorrasc and A Vespignani (2005). Dynamical patterns of epidemic outbreaks in complex heterogeneous networks. J. Theor. Biol. 235, 275–288.

[11] B T Grenfell and F Lutscher (2004). Modeling the dynamics of infectious diseases In A series of PIMS lecture notes.

[12] M J Keeling and J V Ross (2008). On methods for studying stochastic disease dynamics. J. R. Soc. Interface 5, 171-181.

[13] M J Keeling and L Danon(2009). Mathematical modeling of infectious diseases. Br. Med. Bull. 92, 33–42.

[14] A Uziel and L Stone (2012). Determinants of periodicity in seasonally driven epidemics. J. Theor. Biol. 305, 88–95.

[15] N Masuda and P Holme (2013). Predicting and controlling infectious disease epidemics using temporal networks. F1000Prime Reports 5:6 (doi:10.12703/P5-6).

[16] R M Ribeiro and S Bonhoeffer (1999). A stochastic model for primary HIV infection: optimal timing of therapy. AIDS 13, 351-357.

[17] J E Pearson, P Krapivsky and A S Perelson (2011). Stochastic theory of early viral infection: continuous versus burst production of virions. PLoS Comput Biol. 7, e1001058(doi : 10.1371/journal.pcbi.1001058).

[18] N Dalal, D Greenhalgh and X Mao(2009). Mathematical modeling of internal HIV dynamics. Discrete and Continuous Dynamical Systems –Series B 12, 305-321.

[19] G Magiorkinis, V Sypsa E Magiorkinis A Katsoulidou, R Belshaw, C Fraser O G Pybus and A Hatzakis (2013). Integrating phylodynamics and epidemiology to estimate transmission diversity in viral epidemics. PLOS Comp. Biol. (doi : 10:1371/journal.pcbi.1002876).

[20] L C R F Lazhar (2012). Mathematical analysis of nonlinear epidemic models. J Math. Stat. 8, 258-263.

[21] J M Heffernan, R J Smith and L M Wahl (2005). Perspectives on the basic reproductive ratio. J R Soc Interface 2, 281–293.

[22] C Fraser, S Riley, R M Anderson and N M Ferguson (2004). Factors that make an infectious disease outbreak controllable. PNAS 101, 6146-6151.

[23] A Clinton-Arias, C Castillo-Chavez, L M A Bettencourt, A L Lloyd and H T Banks (2009). The estimation of the effective reproductive number from disease outbreak data. Math. Biosci. Eng. 6, 261-282.

[24] H Gaff and E Schaefer (2009). Optimal control applied to vaccination and treatment strategies for various epidemiological models. Math. Biosci Eng. 6, 469-492.

[25] E Hansen (2011). Applications of optimal control theory to infectious disease modeling. Ph. D. thesis, Queen's University, Kingston, Ontario, Canada.

[26] B Buonomo and D Lacitignola (2011). On the backward bifurcation of a vaccination model with nonlinear incidence. Nonlinear Analysis: Modeling and Control 16, 30–46.

[27] M E Alexander, S M Moghadas, P Rohani and A R Summers (2005). Modeling the effect of a booster vaccination on disease epidemiology. J. Math. Biol. (doi : 10.1007/s00285-005-0356-0).

[28] H Hethcote, M Zhien and L Shengbing (2002).Effects of quarantine in six endemic models for infectious diseases. Math. Biosci. 180, 141–160.

[29] A. Fall, A. Iggidr, G Sallet and J J Tewa (2007).Mathematical modeling of natural phenomena. Epidemiology 2, 55–73.

[30] C A A Beauchemin and A Handel (2011). A review of mathematical models of influenza A infections within a host or cell culture: lessons learned and challenges ahead. BMC Public Health 11, S7 (http://www.biomedcentral.com/1471-2458/11/S1/S7).

[31] R Olinky, A Huppert and L Stone (2008).Seasonal dynamics and thresholds governing recurrent epidemics. J. Math. Biol. 56, 827–839.

[32] D Kirschner, V DiRita, and J A Flynn (2005).Overcoming Math Anxiety: Malthus Meets Koch Mathematical modeling helps us to understand host-microbe interactions, including pathogenesis. ASM News 71, 357-362.

[33] ] R Ke, J Aaskov, E C Holmes and J O Lloyd-Smith (2013). Phylodynamic analysis of the emergence and epidemiological impact of transmissible defective dengue viruses. PLOS Pathogens (doi : 10:1371/journal.ppat.1003193).

[34] H Chi, H F Liu, L C Weng, N Y Wang, N C Chiu, M J Lai, Y C Lin, Y Y Chiu, W S Hsieh and L M Huang (2013).Molecular epidemiology and phylodynamics of the human respiratory synctial virus fusion protein in Northern Taiwan. PLOS One (doi : 10. 1371/journal.pone.0064012).

[35] ] A V Melnik and A Korobeinikov (2011).Global asymptotic properties of staged models with multiple progression pathways for infectious diseases. Math. Biosci. Eng. 8, 1019-1034.

[36] A B Gumel, C C McCluskey and P van der Driessche (2006).Mathematical study of a staged progression HIV model with imperfect vaccine. Bull. Math. Biol. 68, 2105-2128.

[37] J H Hyman, J Li, E A Stanley (1999). The differential infectivity model and staged progression models for the transmission of HIV. Math. Biosci. 155, 77-109.

[38] P M Luz, C J Struchiner and A P Galvani (2010) Modeling transmission dynamics and control of vector-borne neglected tropical diseases PLoS Negl Trop Dis 4, e761. (doi:10.1371/journal.pntd.0000761).

[39] Y Xue and X Wang (2012). Global stability of a SLIT TB model with staged progression. J. Appl. Math. Article ID 571469 (doi:10.1155/2012/571469).

[40] E van Kleef, J V Robotham, M Jit, S R Deeny and W J Edmunds (2013).Modeling the transmission of healthcare associated infections: a systematic review. BMC Inf. Dis. 13, 294. (http://www.biomedcentral.com/1471-2334/13/294).

[41] A Alfaro-Murilloa, S Towers and Z Feng (2013).A deterministic model for influenza infection with multiple strains and antigenic drift. J. Biol. Dynamics 7, 199–211.