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A Critical Review in Infectious Disease and Mathematical Modelling

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Abstract

Infectious diseases control and prevention relies on a thorough understanding of the factors determining transmission. The transmission dynamics of infectious diseases is susceptible to changes governed by several factors, whose recognition is critical for the rational development of strategies for prevention and control, as well as for developing health policies. This article summarizes the fundamental principles of infectious disease transmission and compartmental models. Basic principles of infectious disease diagnosis, reasons for formulating the infectious diseases and historical facts on epidemics are also reviewed.

Keywords: Epidemic, Epidemiology, Infectious disease, Transmission, Compartmental Model.

1. Introduction:

An infectious disease is an illness due to a specific infectious (biological) agent or its toxic products capable of being directly or indirectly transmitted from man to man, from animal to man, from animal to animal, or from the environment (through air, water, food, etc.) to man. Human infectious diseases are caused by pathogenic micro-organisms such as bacteria, viruses, parasites and fungi that spread directly or indirectly via a vector from one person to another or from an animal to people.

The effectiveness of improved sanitation, antibiotics, and vaccination programs created a confidence in the 1960's that infectious diseases would soon be eliminated. Infectious diseases have continued to be the major causes of suffering and mortality in developing countries. Moreover, infectious disease agents adapt and evolve, so that new infectious diseases have emerged and some existing diseases have re-emerged [8, 9, 10]. These diseases are a leading cause of death worldwide. Despite all the advancement in medicines, infectious disease outbreaks still pose a significant threat to the public health and economy. The spread rates of different infectious diseases are rising due to changes in human behavior, inappropriate use of antibiotic drugs, increased trade and travel, larger and denser cities and the emergence of new and

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resurgent pathogens. Furthermore, the transmission interactions in a community are very complicated and it is hard to understand the large size dynamics of the spread of the disease without a proper structure of mathematical model [16].

Infectious diseases are the worlds leading cause of death for children and adolescents. They are the second leading overall cause of death after heart disease. Continuous outbreaks of infectious diseases have been reported during the past decade. In the first half of 2014, Ebola caused over 200 deaths in West Africa and over 500 people contracted Middle East Respiratory Syndrome (MERS). There were more than 145 fatal cases of MERS.

Infectious diseases remain the leading cause of death in the world, accounting for about 15 million deaths per year- approximately 25 per cent of total global mortality. The impact is greatest in the developing world. In Africa and South Asia, infectious diseases are the underlying cause of two thirds of all deaths, killing mostly children and young adults. Infectious diseases are also a major cause of permanent disability and poor health and well-being for tens of millions of people, hindering economic development and sustainability in many parts of the world [7].

Although, the great strides have been made, millions of people continue to die each year from infectious diseases and millions more suffer permanent disabilities or poor health. A triple threat is represented by new infectious diseases, the re-emergence of infectious diseases that were once under control, and the continuous development of antibiotic resistance. Along with changes in society and technology and in the microorganisms themselves- these factors are contributing to a perfect storm of vulnerability.

In recent decades, there have been several investigations of infectious diseases using deterministic mathematical models with or without demographic change. In particular, Greenhalgh (1996) has studied an infectious disease model with population-dependent death rate using computer simulation. Gao and Hethcote [6] analyzed an infectious disease model with logistic population growth.

Zhou and Hethcote [17] have studied a few models for infectious diseases using various kinds of demographic. Hethcote has discussed an epidemic model in which the carrier population is assumed to be constant. But in general the size of the carrier population varies and depends on the natural conditions of the environment as well as on various discharges into it by the human population.

Infectious diseases have ever been a great concern of human kind since the very beginning of our history. At present, we still have to deal with plagues and diseases. Millions of people die annually from measles, malaria, tuberculosis, AIDS and billions of others are infected. There was a belief in 1960s that infectious diseases would be soon eliminated with the improvement in sanitation, antibiotics, vaccinations, medical science and medical care. However, they are still the major causes of mortality in the developing countries. Moreover, infectious disease agents adapt and evolve, therefore we can observe new infectious diseases emerging and some already existing diseases re-emerged, sometimes after hundreds of years and/or even mutated.

Together with the threat of biological weapons, whose research is lately concerned about microorganisms and lethal infectious diseases, we have great motivation to understand the spread and control of infectious diseases and their transmission characteristics. Mathematical epidemiology contributed to the understanding of the behavior of infectious diseases, its impacts and possible future predictions about its spreading. Mathematical models are used in comparing, planning, implementing, evaluating and optimizing various detection, prevention, therapy and control programs.

The mathematical study of the transmission of infectious diseases may be regarded as a part of the study of population dynamics. For example, one of the objectives of study is the variation over time of the incidence (number of new cases reported per unit time) of a particular disease within a specified host population. As with other parts of population dynamics, a mathematical model must be formulated which takes into account the most important factors which influence the results. During the present century, mathematicians and biologists have devoted increasing attention to these models.

The spread of a communicable disease involves not only disease-related factors such as the infectious agent, mode of transmission, incubation period, infectious period, susceptibility, and resistance, but also social, cultural, economic, demographic, and geographic factors. Insight into communicable disease processes can be obtained by analyzing models which contain some of these factors [10].

2. Objectives:

The main objectives of this work are as follows:

i. To identify and explain the mechanisms by which infectious diseases may be transmitted to and among humans

ii. To discuss the various procedures by which infectious disease can be transmitted

iii. To find out how to choose the appropriate compartmental model according to the behavior of the infectious disease.

3. Some terms related to the study:

3.1 Pattern of Epidemiology Diseases:

- **Epidemiology:**

The word Epidemiology is derived from Greek words meaning study upon populations (epi-upon, demos-people, logos-study). Epidemiology is the study of health and disease in human population. A broader definition of epidemiology from dictionary of epidemiology has been widely accepted.

According to this definition, epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems [11].

There are three states of epidemiology in used. They are:

(i) Epidemic:

Epidemic is the occurrence of an infectious disease clearly in excess of normal expectancy. It is a sudden outbreak of a disease. When describing an epidemic, the time period, geographical region and particulars of the population in which the cases occur must be specified.

The number of cases needed to define an epidemic varies according to the agent, the size, type and susceptibility of population exposed, and the time and place of occurrence. The identification of an epidemic also depends on the usual frequency of the disease in the area among the specified population during the same season of the year. A very small number of cases of a disease not previously recognized in an area, but associated in time and place, may be sufficient to constitute an epidemic.

The dynamic of an epidemic is determined by the characteristics of its agent and its pattern of transmission, and by the susceptibility of its human hosts. The three main groups of pathogenic agents act very differently in this respect. A limited number of bacteria, viruses and parasites cause most epidemics, and a thorough understanding of their biology has improved specific prevention measures [2].

(ii) Endemic:

Endemic is a habitual presence (usual occurrence) of a disease within a given geographical area. It describes a condition in which a disease always presents. For many endemic infections, the prevalence remains more or less constant over time as long as no changes occur in intervention or prevention strategies.

Many endemic infectious diseases have seasonally fluctuating incidence rates. The seasonality is due to climate conditions, which influence pathogen survival in the environment, and human contact patterns, which fluctuate due to activity patterns (e.g. school holidays). Endemic disease such as malaria are among the major health problems in low-income tropical countries. If conditions change in the host, the agent or the environment, an endemic disease may become epidemic.

(iii) Pandemic:

Pandemic is a worldwide epidemic affecting exceptionally high proportion of the global population and area.

Influenza, commonly known as “the flu“, is an infectious disease caused by the influenza virus. As it presents in the world population in some degree throughout the whole year, so it can be taken as the endemic disease.

Swine flu is a new kind of influenza caused by H1N1 virus. It is a respiratory disease caused by viruses (influenza viruses) that infect the respiratory tract of pigs, resulting in nasal secretions, a barking cough and decreased appetite. The number of infected individuals by swine flu in India recently has reached over 32,233 and 1,911 deaths till the end of March 2015. In Nepal, 42 individuals have been infected and 1 death till the end of February 2015. So, it is now epidemic in India and Nepal.

According to the WHO statistics as of July 2010, the H1N1 virus killed more than 18,000 people since it appeared in April 2009. It had spread more than 40 countries worldwide. However, by 2012, research showed that as many as 579,000 people could have been killed by the disease. So, it is called the pandemic 2009.

3.2 Class of Population:

The total population at any time may be divided into the following three disjoint classes of individuals [12].

(i) Class of Susceptibles:

The susceptible class consists of those individuals who are not yet infected by the disease, but are capable of contacting the disease. Such an individual is called a susceptible.

(ii) Class of Infectives:

The infective class consists of those individuals who have already been infected by the disease and are capable of transmitting the disease to others. Such an individual is called an infective.

(iii) Class of Removals:

The removed class consists of those individuals who have had the disease and are removed from the population by death, isolation or permanent immunity. Such an individual is called a removal.

3.3 Routes of Transmission:

When we talk about an infectious disease, we talk about a communicable disease. It is an illness which arises through transmission of an infectious agent from an infected individual to a host.

• Horizontal Transmission:

An infection can be transmitted through contacts between the infectives and the susceptibles which is known as horizontal transmission. Horizontal transmission refers to the passage of the infection from one host individual to another, for example by inhalation or ingestion of infective material, or else by direct physical contact. The horizontal transmission is assumed to occur according to the mass action incidence. Malaria, dengue fever, bubonic plague are some examples of horizontal transmitted diseases.

• Vertical Transmission:

Vertical transmission is the direct transfer of a disease from an infective parent to an unborn or newly born offspring. Several of the scourges that currently afflict humanity, AIDS, Chagas' disease, Hepatitis B are vertically transmitted. Efforts to control the spread of such diseases require quantitative predictions of the future trends of these infections, and consequently, lead to the construction and analysis of appropriate predictive models that take into account the distinctive aspects of vertical transmission [4].

• Direct Transmission:

Direct transmission is the immediate transfer of the infectious agent from an infected host or reservoir to an appropriate entry point through which human infection can take place. It is a transfer of an infectious agent from the infected individual directly to the host (touching, biting, sexual intercourse etc.). Blood transfusions and transplacental infection from mother to fetus are other important means of direct transmission.

• Indirect Transmission:

It is a transfer of an infectious agent by contaminated inanimate objects (aerosolized agents suspended in air for a long period of time, environment contamination, water/food contamination etc.). It may be vehicle-borne, vector-borne or air-borne. Vehicle-borne transmission occurs through contaminated materials such as food, clothes, bedding and cooking utensils. Vector-borne transmission occurs when the agent is carried by an insect or animal to a susceptible host. Long-distance air-borne transmission occurs when there is dissemination of very small droplets to a suitable point of entry, usually the respiratory tract. Dust particles also facilitate air-borne transmission.

Thus, it is important to distinguish between types of transmission when constructing a model for infectious disease, and selecting control methods. Direct transmission can be interrupted by preventing contact with the source; indirect transmission requires different approaches, such as the provision of mosquito nets, adequate ventilation, cold storage for foods or sterile syringes and needles.

Table 1.1: Examples of Transmission Diseases

Direct Transmission	Indirect Transmission
Mucous membrane to mucous membrane- sexually transmitted diseases	Water borne- hepatitis A
Across placenta- toxoplasmosis	”Proper” air borne- chickenpox
Transplant, including blood- hepatitis B	Food borne- salmonella
Skin to skin- herpes type I	Vectors – malaria
Sneezes, coughs – influenza	Objects/fomites-scarlet fever (e.g. toys in a day care centre)

Historical Side on Epidemics:

The history of epidemics is an ever fascinating area. From past to nowadays a lot of people are interested to study diseases development and their influence upon human because of the difficulty of foreseeing possible consequences of the spread of dangerous diseases. The study of epidemic, recently, has come up with a huge number and variety of models and explanations for the spread and cause of epidemic outbreaks.

The first major epidemic which we can find in the records of the history is the Plague of Athens (430 - 428 BC). Epidemics killed millions of people in 14th century. Similarly, 25 million people died in Europe due to Black Death (1347 - 1350 AD). The Black Death virus stayed within the population after the end of the epidemic outbreak and reappeared in Britain in 1665. Its name, Black Death, comes from its symptoms- the black color of the tell-tale lumps that foretold its presence in victims' body and death for the inevitable result. The plague germs were carried by fleas which lived as parasites on rats. The islands were never totally free of the plague (the plague stayed within the population on the endemic level). This time it was different, the virus mutated. The plague killed more than 100,000 people in the town of London during the next epidemic strike [1, 3].

Another disastrous epidemic attacked Aztecs' population in 16th century- Smallpox plague killed 35 million. A terrible influenza pandemic occurred after the First World War and killed 20 million population in 1919. At present, there are more outbreak history of epidemics- 1905- 1906 the Bom- bay plague, 2003 SARS in Singapore (Severe Acute Respiratory Syndrome). Recently Coronavirus Disease (COVID 19) outbreak throughout the world. According to WHO (World Health Organization), this pandemic has affected more than 760 million population and killed more than 6.9 million population of the world. We have also threats of epidemics as the viruses mutate very quickly.

Although, the epidemiology itself has long history, mathematical study of diseases and their spreading is at most just over three hundred years old. It all started in 1662 when John Graunt published his "Natural and Political Observations made upon the Bills of Mortality". In his book, he has discussed various demographic problems of seventeenth century Britain. He made observations on the death records and calculated risks of death concerning certain disease. Graunt's analysis of the various causes of death provided the first systematic method for estimating the comparative risks of dying from the plague as against other diseases. This is the first approach to the theory of competing risks which is now used in modern epidemiology.

A century later, Daniel Bernoulli showed more theoretical approach to the effects of a disease. The earliest account of the mathematical modeling of the spread of a disease was carried out in 1766 by Daniel Bernoulli. Trained as a physician, Bernoulli created a mathematical model to defend the practice of inoculating against smallpox [10]. The calculations from this model showed that universal inoculation against smallpox would increase the life expectancy from 26 years 7 months to 29 years 9 months. D'Alembert developed in 1761 an alternative method for dealing with competing risks of death, which is applicable to non-infectious diseases as well as to infectious diseases.

In middle 1800s, Louis Pasteur confirmed experimentally the germ theory of the disease and he created the first vaccine for rabies. At the same time, Robert Koch became famous for the discovery of the anthrax bacillus (1877), the tuberculosis bacillus (1882) and the cholera vibrio (1883) and for his de- velopment of Koch's postulates. Pragmatic approaches were limited and there was appropriate theory to explain the mechanism by which epidemics spread. The idea of passing on a bacterial disease through contact between an infected and healthy individual became familiar.

Modern mathematical biology begins with Hamer. He, in 1906, first applied the Simple Mass Action Principle for a deterministic epidemic model in discrete time. Ross's simple Epidemic Model was published in 1911 and Generalized Epidemic Model produced by Kermack and McKendrick [13, 14, 15] in 1927. These models have deterministic character and are still widely used although new models were created taking into consideration various factors like migration, vaccination and its gradual loss, chemotherapy, quarantine, passive immunity, genetic heterogeneity, non-uniformly distribution of population etc.

4. Reasons for Mathematical Modeling of Infectious Diseases:

A disease is infectious if the causative agent, whether a virus, bacterium, protozoa, or toxin, etc., can be passed from one host to another through modes of transmission such as direct physical contacts, aerial droplets, water or food, disease vectors, mother to newborns etc.

The objective of a mathematical model of an infectious disease is to simulate the transmission process of the disease, which can be described generally as follows- when infectious individuals are introduced into a group of susceptibles, the disease is passed to other individuals through its modes of transmission, and the disease spreads in the group. If the number of infected individuals explodes in a short period of time, an epidemic occurs. Infected individuals recover from infection, either through treatment or due to action of the immune system, and gain various degree of acquired immunity against the infection. When the pool of susceptible individuals is depleted, new infections will stop, and the epidemic slows down and stops. If fresh susceptibles are added to the group, either from birth or migration, or if the reinfection is easy, then epidemic may last very long, and the infection may persist in the group over a long period of time. In this case, the disease is said to be endemic in the group. If the disease spreads to a large geographic area, far beyond the location of initial occurrence, we say that a pandemic occurs.

Why is mathematical modeling of infectious diseases useful? Part of the reason is that traditional methods using experimental and statistical approaches may not be adequate for various aspects:

- Infectious diseases often affect a large population of individuals over a large geographic area. Experiments conducted in laboratories are often inadequate simply because of the huge difference in scales.

- For infectious diseases of humans, large scale experiments may be impossible or unethical.
- Existing data sets about the disease may not be complete or accurate for the statistical analysis to be reliable.

By comparing the model outcomes with existing knowledge or data of the disease, we can use the model to test various hypotheses about the disease. There are often many issues associate with mathematical modeling:

- Due to our limited knowledge about infectious disease, realistic assumptions about its transmission process are not always possible.
- Model validation using disease data may be difficult.
- Mathematical analysis of the model may be limited by the existing mathematical theory.

There is always a trade-off in mathematical modeling between more realistic models and our ability to analyze mathematically the model and obtain useful informations.

5. Compartmental Models:

Mathematical modeling has provided researchers with more knowledge about real world systems. Mathematical models are used in many disciplines including physics, chemistry, biology, engineering, economics, and computer science, among many others. Anything that changes can be modeled mathematically. These models provide better understanding to the physical components of the system and allow the researcher to make better predictions about the system's behavior.

Mathematical modeling has become a valuable tool to understand the dynamics of infectious disease and to support the development of control strategies. A lot of mathematical models for different infectious diseases were proposed by several researchers and scientists. The emerging and reemerging diseases have led to a revived interest in infectious diseases. Mathematical models have become important tools in analyzing the spread and control of infectious diseases.

The model formulation process clarifies assumptions, variables, and parameters; moreover, models provide conceptual results such as thresholds, basic reproduction numbers, contact numbers, and replacement numbers. Mathematical models and computer simulations are useful experimental tools for building and testing theories, assessing quantitative conjectures, answering specific questions, determining sensitivities to changes in parameter values, and estimating key parameters from data. Understanding the transmission characteristics of infectious diseases in communities, regions, and countries can lead to better approaches to decreasing the transmission of these diseases.

Mathematical models are used in comparing, planning, implementing, evaluating, and optimizing various detection, prevention, therapy, and control programs. Epidemiology modeling can contribute to the design and analysis of epidemiological surveys, suggest crucial data that should be collected, identify trends, make general forecasts, and estimate the uncertainty in forecasts.

One of the most basic procedures in the modeling of diseases is to use a compartmental model, in which the population is divided into different groups. A compartmental model is one for which the individuals in a population are classified into compartments depending on their status with regard to the infection under study. They are usually classified by a string of letters that provides information about the model structure. Compartments with labels such as M, S, E, I and R are often used for the epidemiological classes.

The choice of which compartments to include in a model depends on the characteristics of the particular disease being modeled and the purpose of the model. The passively immune class M and the latent period class E are often omitted, because they are not crucial for the susceptible-infective interaction. Acronyms for epidemiology models are often based on the flow patterns between the compartments such as MSEIR, MSEIRS, SEIR, SEIRS, SIR, SIRS, SEI, SEIS, SI, and SIS [10]. We will discuss about few of the above models.

5.1 **SI Model:**

The SI Model is the simplest one among the epidemic models. That is why it is also called the Simple Model. We divide the population just in the susceptible compartment S(t) and the infectious compartment I(t). We do assume the disease to be highly infectious but not serious, which means that the infectives remain in contact with susceptibles for all time $t \geq 0$. We also assume that the infectives continue to spread the disease till the end of the epidemic. Infection rate is proportional to the number of infectives.

SI models are useful for some plant infections since they remain infected until they die. Spread of head lice in human population with no means of effective treatment would also fit the SI-model.

The SI-Model equation is

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI$$

where β is the rate of transmission and S and I are the number of susceptible and infective populations.

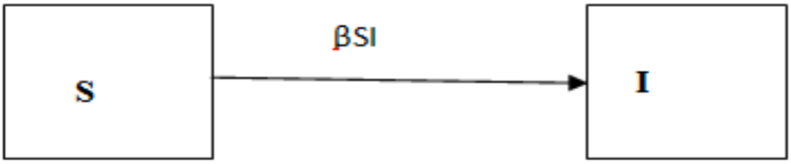

Figure : Transfer diagram of the SI model

5.2 **SIS Model:**

Suppose the total population under consideration is divided into disjoint classes which change with time t. The susceptible class consists of those individuals who can get the disease but are not yet infective. The infective class consists of those who are transmitting the disease to others. The remove class consists of those who are removed from the infective by recovery with immunity, isolation or death.

If recovery does not give immunity, then the model is called SIS model, since individuals move from the susceptible class to the infective class and then back to the susceptible class upon recovery. SIS models are appropriate for some bacterial agent diseases such as meningitis, plague and venereal diseases and for protozoan agent diseases such as malaria and sleeping sickness. SIS models are also appropriate for some diseases, in particular sexually transmitted diseases like gonorrhoea, because once recovered, the host is once again susceptible to infection.

The SIS-Model equation is:

$$\frac{dS}{dt} = -\beta SI + \gamma I$$
$$\frac{dI}{dt} = \beta SI - \gamma I$$

where β is the rate of transmission, γ is the rate of infection and S and I are the number of susceptible and infective populations.

Figure : Transfer diagram of the SIS model

5.3 **SIR Model:**

The SIR Model is used in epidemiology to compute the amount of susceptible, infected, and recovered people in a population. It is also used to explain the change in the number of people needing medical attention during an epidemic. It is important to note that this model does not work with all diseases. For the SIR model to be appropriate, once a person has recovered from the disease, they would receive life-long immunity. The SIR model is also not appropriate if a person was infected but is not infectious. The Susceptible-Infected-Recovered (SIR) model is often used to study the spread of infectious disease by tracking the number (S) of people susceptible to the disease, the number (I) of people infected with the disease, and the number (R) of people who have had the disease and are now either recovered or dead. The SIR model is a classical model in mathematical epidemiology.

The SIR-Model equation is:

$$\frac{dS}{dt} = -\beta S \frac{1}{N}$$

$$\frac{dI}{dt} = \beta S \frac{1}{N} - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

The parameter is the rate of infection and is called the transmission coefficient. The parameter is called the removal or recovery rate and its reciprocal determines the average infectious period.

Figure : Transfer diagram of the SIR model

6. Conclusion:

It is all the more important that we have the tools needed to understand transmission dynamics and implement effective prevention and control programs. Clear definitions of terminology and elucidation of fundamental principles lay the foundation for effective public health interventions. Compartmental models have provided valuable insights into the epidemiology of many infectious diseases. This paper provides an introduction to modeling infectious disease dynamics with a focus on several possible problems. We attempt to show when these issues are likely to arise and how to proceed with models and analyses despite them. This paper is intended to serve as a supplement for the many excellent texts on infectious disease dynamics and it provides a concise reference that compiles a range of common issues in disease modeling.

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