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Review Article

Models to predict H1N1 outbreaks: a literature review

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ABSTRACT

With high mortality and panic association, policy- makers face the difficult task of making appropriate and timely decisions to mitigate the serious adverse effects over a short period of time during H1N1 influenza outbreak. Mathematical models predict the number of the cases and thus provide an insight for preparedness during outbreak. The objective was to identify various mathematical models used in prediction of H1N1 outbreaks till date and to compare the usefulness of these models in providing magnitude of H1N1 outbreaks. Hence a secondary data analysis of literature review was done. The literature search was conducted using PubMed and Google scholar, restricting it to articles published until May 2015. The key parameters were set for selection of articles and hence a total of 31 articles has been reviewed. Of each article included in the review, the following data was recorded: year of the study, year of pandemic referring to, country, described mathematical model with results of study The SEIR model is most commonly used mathematical model. SIER model takes all factors in a epidemic phase of an individual i.e. Susceptible – Exposed – Infective – Recovered. While studies which utilised SIER model with the combination of other models found the other factors which influence the occurrence of H1N1 outbreaks and also helped in prediction and prevention of number of cases during outbreak. The SEIR models in combination utilised secondary models such as social networking, global network and total layered containment. The literature review suggests that probable use of mathematical model along with some secondary models will help in better prediction and prevention of number of cases during outbreak.

Keywords: H1N1, Mathematical models, SIR model, SIER model

INTRODUCTION

Influenza is an international disease as it occurs in all countries and affects millions of people every year. Influenza is a acute viral infectious disease of the respiratory tract which presents with fever, chills, generalised feeling of weakness and pain in the muscles with varying degrees of soreness in the head and abdomen. Influenza belongs to the family of Orthomyxoviridae and is Ribonucleic acid (RNA) virus. The virus is divided into three main types i.e. A, B, and C. These types are identified by differences in two major internal proteins ie hemagglutinin (HA) and neuraminidase (NA).

Influenza type A is the most dangerous among the three varieties. It infects a wide variety of birds and also mammals. It causes the most number of disease cases among humans and is the type which most likely to become an epidemic. Influenza type B infects humans and birds which produce a milder variety of disease that can cause epidemics. Type C infects only humans. It is known typically to produce a very mild illness which is not different from a common cold or sometimes may not produce any symptoms at all. Type C does not cause epidemics. Influenza A is divided into subtypes on the based on differences in the membrane proteins hemagglutinin (HA) and neuraminidase (NA). These are the most important targets for the immune system. Influenza type A has 16 hemagglutinin subtypes from H1 to H16 and 9 neuraminidase subtypes from N1 to N9 known in birds. Only H 1, 2, and 3 and N 1, 2, are commonly found in humans. Currently two subtypes are known to be circulating in humans H1N1 and H3N2. The Subtypes are again further divided into strains, each of which is genetically distinct virus isolate and is usually considered to be a separate strain. An antigenic shift in the influenza A virus can result in an pandemic affecting most parts of world just within a matter of months. Evidences point towards that all influenza viruses in mammals and humans are derived from viruses which are present among wild ducks and water fowls. Some of these viruses could have been acquired by humans thousands of years ago. But medical historians are not known of any clearly identifiable influenza epidemics until large scale outbreaks which occurred in Europe nations in years 1510, 1557, and 1580. The 1580 outbreak also spread to Asia and Africa making it the first known pandemic. Subsequently major pandemics took place in years 1729 to 1730, 1732 to 1733, 1781 to 1782, 1830 to 1831, 1833, and 1889 to 1890.[1,2]

Mathematical modelling of an epidemic

Mathematical modelling of an epidemic has an important role in understanding the various complexities associated with an infectious disease and its control. It is beneficial in understanding the mechanisms underlying observed epidemiological patterns and assessing the effectiveness of control strategies and also predicting epidemiological trends. Mathematical modelling of human diseases has been from long times. The first mathematical model in epidemiology was prepared by Daniel Bernoulli, a Swiss Mathematician on the effect of variolation against smallpox in increasing life expectancy. His work had idea of differential mortality for estimation of the rate of deaths attributable for a given disease. This has been used to estimate disease death rates of past epidemics like 1918 influenza pandemic. R. A. Ross did modelling on malaria transmission. Ross (1897) showed that malaria was indeed transmitted through mosquitoes and hence developed model to describe the spread of malaria. He concluded from his model that by reduction in the mosquito population could control malaria in a given region. Then in 1927 Kermack WO and Mckendrick AG (1927), published paper on contribution to the mathematical theory of epidemic. A simple deterministic/compartmental model of susceptible – infectious – recovered (SIR) model was first used for explaining the behaviour of the plague and cholera epidemics e.g. Cholera epidemic in London 1865.

The important concepts in modelling outbreaks of infectious diseases are the a) basic reproductive number, universally denoted by $R_{0,}$ and b) the generation time i.e. the average time from onset of symptom in a primary case to onset of symptom in a secondary case. This will determine the likelihood and speed of epidemic outbreaks.[3-7]

Epidemiologists define R_0 as “the average number of secondary cases produced by a typically primary case in an entirely susceptible population”. This forms a basic concept in mathematical epidemiology which is derived originally by theoretical modelling assumptions, considerations and then verified in observations. The calculations for a given model with its estimation from observations are important in the analysis of models and also in interpretation of data. If $R_o>1$, the disease can enter a complete susceptible population and hence number of cases will increase. If $R_o<1$, the disease will fail to spread in population. Hence this tells us whether a population is at risk from a given disease. Many epidemiological researches are presented in terms of basic reproduction number.

Till date various mathematical models have been proposed to predict the occurrence of H1N1 across the globe. But there has been few studies done which could bring all the various mathematical models together and analyse them. This study is innovative in analysing the mathematical models used in H1N1 epidemics not only used in India but also other countries. So this research attempts to study and analyse various mathematical models used in H1N1 prediction and occurrence.

Review of literature

Following is the review of related works on past influenza pandemics and 2009 influenza A (H1N1) modeling.

Epidemiological mathematical modelling methods

There has been different classification of types of mathematical modelling

Classification (A) suggests that there are two types of epidemiological modeling technique:

1. Stochastic (probabilistic) and
2. Deterministic (compartmental models, non probabilistic)

E.g. Susceptible – infective (SI), Susceptible – Infective – Susceptible (SIS), Susceptible–Infective–Recovered (SIR), Susceptible–Infective–Quarantine-Recovered (SIQR), Maternally–derived immunity–Susceptible-Infective–Recovered (MSIR), Susceptible–Exposed–Infective–Recovered (SEIR) and Carrier State Model.

The other classification i.e. (B) is simple mathematical model and advanced mathematical models**.**

A. *Simple mathematical model*

The basic mathematical model SIR or Susceptible-Infected-Recovered was developed by Kermak and Mckendrik in 1927.[5] A simple mathematical model has the following assumptions:

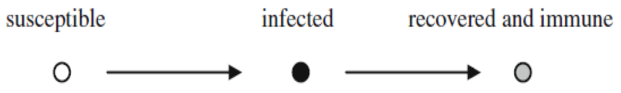

Figure 1: Transition of an infected individual Wallinga.[8]

1. The total population is taken as a constant.
2. An initial infected population is introduced to the total population.
3. The spread of disease to rest of population is described as a function of time.
4. The dead or recovered people in the community are counted together.

In mathematical terms, the total population can be divided to three different classes : susceptible S, who has the chance of getting infected, the infected I who represents the infected population and removed R, those who have been recovered, dead, immune or isolated until recovered. The total population can be represented as

$$S \rightarrow I \rightarrow R$$

These models are referred to as Susceptible-Immune-Removed or SIR models.

Several extensions have been made to the SIR model such as SEIR Susceptible exposed Infected Removed adding exposed stage for the latent diseases. The SIR model can be described as a function of time, that is $S(t)$, $I(t)$ and $R(t)$.

The SIR model has many assumptions about the equations such as

1) The increase in the infected class is proportional to number of infective and susceptible that is rSI, where r is constant.
2) The rate of removal of infective to removed class is proportional to number of infective that is aI, where a is constant and 1/a is the time spent as infected.
3) The incubation period is negligible or in other words the infected person becomes infectious in no time.
4) The population is uniformly mixed.

The total population can be represented in three differential equations

$$dS/dt = -r\,SI$$
$$dI/dt = rSI - aI$$
$$dR/dt = aI\,dt$$

where $r>0$ is the infection rate and $a>0$ is the removal rate [Kermak and McKendrik (1927)]. Adding the equations (1), (2) and (3).

The total population is represented by

$$dS/dt + dI/dt + dR/dt = 0 \Rightarrow S(t) + R(t) + I(t) = N$$

where N is the total population. The mathematical formulation is complete with the conditions $S(0)>0$, $I(0)>0$ and $R(0)>0$. The relative removal rate is called as contact rate. The initial conditions for the curve are $I(0) = I0$ and $S(0) = S0$. With $R(0) = 0$, all trajectories start on the line $S + I = N$ and retain inside the triangle since $0<S + I<N$ for all time.

The basic reproduction rate Ro is defined as $R_0 = rS_o/a$

The reproductive rate in other words is the number of secondary infection produced by the primary infection introduced into the total susceptible population.

1/a is the infectious period. The calculation of reproductive rate is crucial in finding whether the epidemic is under control.

B. *Advanced mathematical models*

Mathematical models have been modified adding intermediate stages and structure to describe the dynamics of disease spread. Kretzschmar and Wallinga classifies the advanced mathematical models into following subsections.[8]

1. *Stochastic models*

Stochastic models or models using probability distribution to predict outcomes are also used as a variation of the basic SIR mathematical model. Though in the basic model the stochastic effects are not considered, in stochastic variation, probabilities describe transition between the states. Stochastic simulations have been using Monte-Carlo simulation and Reed-Frost models [Bailey (1975)].

2. *Continuous age models*

Continuous age models were defined in terms of mathematical equations using partial differential equations. When compared to ordinary differential equations, partial differential equations are difficult to implement.

3. *Complex compartmentalised models*

Additional features such as latent period, vaccinated population were also added to mathematical system SIR for disease dissemination Anderson and May and Diekmann and Heesterbeek.[6,7] Instead of uniform mixing of population groups, heterogeneity was added to population. The model was used to model disease spread among sexual partners during an HIV/AIDS pandemic. Adding age structure was also done to the basic model which requires various age compartments with people passing from one age rate to other.

Aims and objectives

The aim is to study various mathematical models used to predict H1N1 outbreaks around the world. And the objectives are 1) To identify various mathematical models used in prediction of H1N1 outbreaks till date. 2) To compare the usefulness of these models in providing magnitude of H1N1 outbreaks.

METHODS

Design of study

Secondary data analysis / literature review of various mathematical models available for H1N1 Influenza.

The literature search was conducted using PubMed and Google scholar, restricting it to articles published until May 2015. Five Different sets of keywords were being considered. i.e. Mathematical model for H1N1, Deterministic model for H1N1, Probabilistic Model for H1N1, Stochastic epidemic model for H1N1, Compartmental model for H1NI. A systematic selection procedure was conducted in two steps

In the first step, the major topics of the articles were assessed by title and abstract. In this phase of the selection procedure, all articles reporting mathematical models on influenza pandemics and outbreaks (H1N1) were included. In case of doubt on the article's relevant information, the article was included in the second selection step.

In the second step, the full text articles, previously selected were be assessed. These articles were included in the review if they reported at least one of the following parameters:

1) Basic reproduction number (R0) for H1N1
2) SIER model for H1N1
3) SIS model for H1NI,
4) SER model for H1N1
5) SIQR Model for H1N1
6) MSIR model for H1N1

If the articles did have any information on at least one of the parameters listed above or if the study design was of good quality and is included.

Of each article included in the review, the following data will be recorded: year of the study, year of pandemic referring to, country, described mathematical model with results of study.

RESULTS

This section deals with the results of the following secondary data literature review.

A total number of 124 articles were selected in first step i.e. based on Title and abstract. Then based on the selection parameters 31 articles were selected.

Table 1: Showing name, year, pandemic referring to, county, and described mathematical model and any secondary model used in study.

Name of study	Year of study	Year of pandemic referring	Country study is done	Described mathematical model	Any secondary model used
Chowell et al[9]	2007	1918-1919	Towns and Rural Areas of England and Wales	SIR Model	
German et al[10]	2006	1917-1918	United States of America	SIR Model	
Mills et al[11]	2004	1918-1919	United States of America	SIER Model	
Yoneyama and Krishnamurthy[12]	2010	1918-1919	Belgium, Canada, France, Germany, Ireland, Italy, Mexico, Portugal, Spain, United Kingdom, and the United States.	SIER Model	Social networking
Chowell et al[13]	2007	1918-1919	California, USA	Early Exponential growth rate, simple SIER model, an complex SIER Model, Stochastic SIR model with Bayesian estimation.	
Yoneyama and Krishnamurthy[14]	2010	1957-1958		SIER Model	Network model (global connection)
Wu et al[15]	2006	1976	USA	SIS model	

Bootsma and Ferguson et al[16]	2007	1918	USA	SIER Model	Social distancing
Halloran et al[17]	2008	1976	USA	SIR Model	Total layered containment
Longini et al[18]	2004	1976	USA	SIR Model	
Boelle et al[19]	2009	2009	Mexico	SIER Model	
Fraser et al[20]	2009	2009	Mexico	SIS, SIR,SIER	
Boelle et al [21]	2009	2009	52 major cities across world	SIER Model	
Boni et al[22]	2009	2009	Vietnam	SIER model	
Cauchemez et al[23]	2009	2009	USA	SIS Model	
Gojovic et al[24]	2009	2009	Ontario, Canada	SIER Model	Social distancing
Ferguson et al[25]	2009	2009	Mexico	SIER Model	
Mei et al[26]	2010	2009	China	SIER Model	Bayesian correction
Gu Y et al[27]	2011	2009	Japan	SIER Model	
Towers and Feng[28]	2009	2009	USA	SIR Model	
Massad et al[29]	2010	2009	Brazil travellers to Chile, Argentina, USA	SIR Model	
Lee et al[30]	2010	2009	USA	SIR Model	Social distancing
Suh et al[31]	2010	2009	South Korea	SIER Model	Social distancing
Hsieh et al[32]	2010	2004-2005	Taiwan	Compartment model	
Shil et al [33]	2011	2009	India	SIER Model	
Li et al[34]	2011	2009	China	SIER Model	Gravity model
Poletti et al[35]	2010	2009	Italy	SIER Model	Cost/Benefit analysis
Shiv Dutt et al[36]	2011	2009	India	SIR Model	
Jumpen et al[37]	2011	2009	Canada	SIS Model	SEIQR model
Sharomi et al[38]	2010	2009	Manitoba, Canada	SIR Model	

Table 2: Showing mathematical models with number of studies along with advantages and disadvantages.

Mathematical Model	No. of studies	Advantages of model	Disadvantages of model
SIS Model	3	Simple and easy to use	Does not include all factors of epidemic modelling i.e. recovered
SIER Model	9	Provides reliable prediction of cases during outbreak	Complex, assumptions required for modelling
SIR model	9	Simple and Easy to use	Does not include factor of epidemic modelling of exposed
Compartmental model	1	Provides reliable prediction of cases during outbreak	Complex and requires assumptions to be made prior to modelling
Combined model with SIER (two models only)	7	Most predictable method of prediction of cases during outbreak. Takes other factors associated with modelling in to account	Complex and requires adequate time and training to prepare the combined mathematical model
Early exponential growth rate, simple SIER model and complex SIER model, Stochastic SIR model	1	Use of more than one model helps in prediction of number of accurate cases during outbreak	Requires adequate time and skills to analyse the various models
SIS, SIR, SIER	1	Use of more than one model helps in prediction of number of accurate cases during outbreak	Requires adequate time and skills to analyse the various models
Total	31		

The Table 1 shows name, year, pandemic referring to, county, and described mathematical model and any Secondary Model used in study. The mathematical modelling has been done on various outbreaks of H1N1 epidemic around the world. The variety of simple and complex mathematical models has been used. There are single as well as combination of two or combination of multiple models. There have been combined models used along with some primary model or two or more models are used in combination.

The Table 2 shows various mathematical models which were used among studies in the literature review. The most common used model is SIER model i.e. 9. There are also 7 SIER models combined with other secondary model like social distancing, SEIQR model, Social Networking model, Gravity model and cost benefit analysis. The next most commonly used model after SIER model is SIR model i.e. 9. The other models also used are SIS models, Compartmental Model, a combination of SIS, SIR and SIER with 3, 1 and 1 respectively.

DISCUSSION

Based on the selection parameters of the methodology the studies with mathematical modelling conducted from 2004 to 2011 of various H1N1 outbreaks were 31. The various models used are a simple SIS model, SIR mode, SIER model and an combination of SIER model with other secondary model or a multiple mathematical model. Some studies utilised mathematical models empirically present in textbook with no modification (German et al, Mills et al, Boni et al) while some utilised with some modifications like use of secondary models (Yoneyama and Krishnamurthy et al, Bootsma and Ferguson, Lee et al, Shu et al).[10,11,14,16,22,30,31]

The commonly used mathematical model among all is SIER model as it takes all factors of an epidemic phase of an individual i.e. Susceptible – Exposed – Infective – Recovered. While studies which utilised SIER model with the combination of other models found that the other factors which influence the occurrence of H1N1 outbreaks and also in prediction and prevention of number of cases during outbreak. The study done by Yoneyama and Krishnamurthy used SIER model with Social networking.[12] This social networking included data on both civil and military traffic. Similarly simulation of another identical scenario where there was no military traffic during pandemic so to determine the influence of war on the pandemic. The results of simulation study showed that among the countries which were involved in the war, the infections were much influenced in them and while countries which were not much engage in the war the infections were not influenced by the war. Similarly the study done by Halloran et al included SIR model with set of potentially feasible intervention strategies combinations called total layered containment (TLC).[17] Total layered containment included influenza antiviral treatment, prophylaxis and non-pharmaceutical interventions such as school closure, quarantine, isolation, community and workplace social distancing. This study suggested that combination of model helps in prediction of number of cases along with the timely implementation of a targeted household antiviral prophylaxis along with non-pharmaceutical intervention like social distancing could substantially lowered the illness attack rate even before a highly efficacious vaccine could become available. The study also concluded that timely initiation of intervention measures and school closure also play an important role in lowering the attack rate.

Yoneyama and Krishnamoothy study 2010 with SIER model with Global network modelled the spread of the 1957 to 1958 influenza pandemic with consideration of the effect of cold war in nineteen countries by using the SEIR and network model.[12] The SEIR model was used for local areas and the network model was used for global connection between countries. The simulation study took into consideration international relationship among different nineteen countries in different years. The results of study showed that the impact of pandemic in each country was influenced by international relations. Similar secondary models along with mathematical models used are Bootsma et al SIER with social distancing, Lee et al SIR model with social distancing.[16,30]

Li et al used the SIER model with gravity model to predict the spread of influenza A (H1N1) worldwide and its relationship with socio–economic indicators such as population size, per capita gross domestic production (GDP), and distance between countries and states through the estimation of parameters of a generalized linear model.[34] The gravity model considers the effect of distance and the size of the donor and recipient communities. They concluded that the gravity model is valid if the spread period is long enough for estimating the model parameters.

Poletti et al. analyzed the 2009 influenza epidemic in Italy by using SIER model with cost/benefit analysis to understand whether spontaneous behavioural changes in the population could be responsible for the epidemic spread.[35] The performed investigation revealed that an initial overestimation of the risk of infection in the general population possibly induced by the high concerned for the emergence of a new influenza pandemic results in a pattern of spread compliant with the observed one. By assuming a generation time of 2.5 days, the initial diffuse misperception of the risk of infection led to a relatively low value of the reproductive number 1.24 which increased to 1.48 in the subsequent phase of the pandemic. They concluded that spontaneous behavioural changes in the population not accounted by the large majority of influenza transmission model cannot be neglected to correctly informed public health decisions. Individual choices can drastically affect the epidemic spread, by altering timing, dynamics and overall number of cases.

CONCLUSION

The literature review suggests that probable use of mathematical model along with some secondary models will help in better prediction and prevention of number of cases during outbreak.

Limitations

The study was not able to statistically justify the best mathematical model in modelling of H1N1 epidemic due to lack of sufficient data to analyse, even though it suggested that use of combination of one or more mathematical model would be more suitable and acceptable.

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