A Way Forward for the Evaluation of Health Technologies for Infectious Diseases

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Recently, many researchers undertaking health technology assessment of screening or vaccination programs for infectious diseases have opted for dynamic transmission models for their analysis, rather than the typical static models (Markov and decision tree), as they are better at predicting the indirect effects of interventions, such as those that may affect disease transmission within the interested population or the ecology of the pathogen. Nevertheless, these models have not yet become part of the traditional tool box of health economists, due in part to the fact that the results are complex and difficult to analyze, requiring extensive computational skills. This paper aims to provide an overview of the concept of a dynamic transmission models and outline recommendations on how best to determine whether a dynamic approach is appropriate when evaluating health technologies and interventions for infectious diseases.

Keywords: *Technology assessment, Cost-benefit analysis, Dynamic transmission model, Infectious diseases, Vaccines*

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Since the mid-1990s, the number of studies on the evaluation of health technologies and interventions related to infectious diseases has increased significantly[1]. This rise in interest seems to have been the result of a number of changes that occurred in the last two decades, including the rising incidence and spread of certain infectious diseases, better understanding of the causes of various infectious diseases, and above all, the development of novel vaccines that can be used to prevent infection. One recent systematic review showed that, of the economic evaluation studies published between 1990 to 2009, the proportion of economic evaluations that examined infectious diseases rose from 8% to 13%, with most of these evaluating vaccines[2]. Vaccination programs, especially universal vaccination programs, are widely regarded as worthwhile interventions, and their use in public health programs is often assumed to be cost-effective[3]. However, whether a vaccination program is cost-effective will depend on a variety of factors, including the efficacy of the vaccine, acceptance rates, prices set, and society's willingness-to-pay. Therefore, the value of such interventions will vary according to the specific context within which the decision-making and implementation is taking place; this can be seen in recent evaluations of vaccines for the Human immunodeficiency virus (HIV) and Human Papilloma virus (HPV), which showed marked differences in value depending on the context of the program[4,5].

Mathematical modelling can be used to simulate the progression of infectious diseases. In the public health arena, these models are usually used to evaluate public health policies by forecasting incidences of emerging diseases resulting from different policy scenarios, such as livestock culls, travel restrictions, school closures, or isolation and quarantine of infected persons/animals. Recently, many researchers undertaking health technology assessment of screening or vaccination programs for infectious diseases have opted for mathematical models (sometimes referred to as dynamic transmission models or dynamic models) for their analysis, rather than the typical static models (Markov and decision tree), as mathematical models are better at predicting the indirect effects of such interventions. However, the use of dynamic models in health technology assessment is relatively new, and these models require inputs from a multidisciplinary standpoint, to ensure that they offer an accurate method for analysis.

The use of these models is becoming increasingly recognised by the international community. The World Health Organisation, for instance, has developed a set of guidelines for economic evaluations

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of immunisation programs, with a chapter outlining a clear justification for the use of static or dynamic models for this purpose[6]. Moreover, the ISPOR-SMDM Modelling Good Research Practices Task Force recently published a set of good practices that should be adopted when using dynamic transmission models for economic evaluations[7,8]. This paper hopes to add to this growing body of evidence and analysis by providing a clear summary of the concept behind dynamic transmission models and by outlining suggestions for the appropriate use of the dynamic approach when evaluating health technologies and interventions for infectious diseases.

Principle of dynamic transmission model

Static models and dynamic models differ predominantly through the way that they use infection rates (force of infection[1]). In static models, infection rates are either constant over time or vary according to personal characteristics such as age. In contrast, the infection rates used in dynamic models depend on the contact pattern, transmissibility, and distribution of the infected population over time, meaning that the infection rate is not constant.

Health technologies that are used in the treatment or prevention of infectious diseases–such as vaccinations–provide individuals with protection against specific infections. Vaccinations also reduce the rate of infection in the community within which those who are vaccinated live, by limiting the risk of an outbreak of the infectious disease. This is true only as long as a critical portion of a given community has been immunized against a contagious disease, which allows the spread of the infectious disease to be contained. This is known as "herd immunity". An example of this can be seen in the eradication of smallpox, which resulted from a global vaccination program[1]. These kinds of indirect effects can be seen not only in vaccination programs but also in health interventions such as the screening and treatment for sexual transmitted diseases[9,10]. However, not all indirect effects resulting from health interventions benefit society. For instance, vaccination programs may also result in negative effects for a society. This can be seen in one case from the UK, where a pneumococcal conjugated vaccine program caused a pathogen strain replacement in the community within which it was implemented as well as in the case where a childhood vaccination program for the varicella-zoster virus resulted in age-shifting, where the disease began breaking out in other age group populations[11,12].

Dynamic transmission models are useful for evaluating technologies that affect disease transmission within the interested population or ecology of the pathogen. If such interventions or technologies do not affect the force of infection, a static model may be used instead.

Model structures

In any economic evaluation, modeling the disease pathway accurately is a crucial step in determining which model is most appropriate. Depending on the natural history of the infection, various "compartments"–more widely known as health states–are defined for the model. These are usually set as susceptible, pre-infectious, infectious, and recovered/immune. The susceptible (S) state represents those who are at risk of infection. The pre-infectious (E) state occurs when an infected person is not yet able to pass the disease on to others but may become infectious in the future, while the infectious (I) state is the state in which a person becomes infectious. The recovered/immune state (R) is where a person becomes immune or has recovered from the infectious state.

As mentioned earlier, to determine which model is most appropriate, a full understanding of the disease pathway is essential. For example, in a case where an individual becomes infected with a disease and is re-infected again, a Susceptible-Infected-Susceptible (SIS) model may be deemed most appropriate. However, if the disease is curable, then a Susceptible-Infected-Recovered (SIR) model may be more appropriate. Examples of disease transmission in infectious diseases are shown in Fig. 1. Transmission models shown in Fig. 1 are appropriate when modeling a disease where transmission is between humans. However, when dealing with diseases that involve non-human hosts (parasites) such as Helminths and Anthropods, a model representing a disease pathway within the non-human hosts may also be necessary[13]. Once a disease pathway has been developed, the next step in developing the model is to identify the pathway of the technology of interest. Where a vaccination program is introduced, those who were previously recognised as susceptible and had been vaccinated would shift to the immune stage, given the vaccine efficacy and coverage. Fig. 2 illustrates the pathway of population shifting from the susceptible compartment to the recovered/immune compartment in the SEIR model.

Once the structure of the transmission disease has been determined, the differential equations to

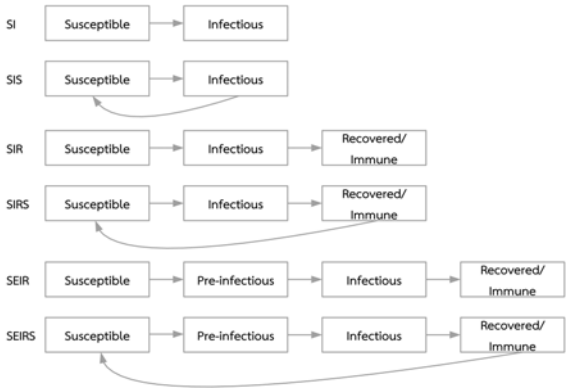

Fig. 1 Common model structures for infectious diseases between human hosts.

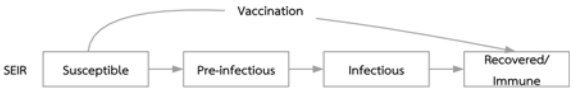

Fig. 2 The disease transmission of an infectious disease when considering vaccination.

represent the transition of the population between each compartment are then defined in order to calculate the population in each compartment at a given point in time. Afterwards, the costs and outcomes of each event are calculated. An example of the set of differential equations for a SEIR model with effect from vaccination in birth cohorts is listed below:

$$\frac{dS(t)}{dt} = b(1-v)N(t) - \lambda(t)S(t) - mS(t)$$

$$\frac{dE(t)}{dt} = \lambda(t)S(t) - fE(t) - mE(t)$$

$$\frac{dI(t)}{dt} = fE(t) - rI(t) - mI(t)$$

$$\frac{dR(t)}{dt} = bvN(t) + rI(t) - mR(t)$$

where,

S(t) denotes the number of susceptible individuals at time *t; E(t)* denotes the number of individuals in the latent period of infection at time *t; I(t)* denotes the number of infectious individuals at time *t; R(t)* denotes the number of individuals who recovered from the disease or were immune at time *t; N(t)* denotes the total population of interest at time *t; b* denotes the birth rate, or the rate at which individuals enter the specific population; *m* denotes the death rate, or the rate at which individuals exit the specific population; *v* denotes the proportion of individuals receiving vaccination; *f* denotes the rate of onset of infectiousness; *r* denotes the recovery rate; and $\lambda(t)$ is the rate at which susceptible individuals become infected per unit time at time *t*, also known as the force of infection. Similar to the development of a typical static model, the identification of input parameters is important. Specific parameters used in the dynamic transmission model are shown below:

Force of infection, $\lambda(t)$

The force of infection is a function of the number of infected individuals in the population and its contact rate between the infected individuals and susceptible individuals:

$$\lambda_t = \beta I_t$$

Where I_t denotes the number of infected individuals at time *t*, and β denotes the ability of successful infections (per capita rate), which depends on the spread of disease. The ability of successful infections depends on the route of transmission (i.e, whether respiratory, sexual, or vector-borne) and the density of the population. For example, a respiratory infection will spread at a higher rate in urban areas compared to rural areas (higher value of β), and a disease is transmitted by mosquitoes, the infection rate is likely to be higher in slum areas than in open-air areas. Other factors such as the age of the population, the distances and frequency of population travel within the area also play an important role. Therefore, it is difficult to obtain β directly. Instead, it is calculated using the formula below, given that the individual in the population mixes randomly:

$$\beta = \frac{R_0}{ND}$$

N is the total population and *D* is the amount in time for disease spread; R_0 is the basic reproduction number, meaning the average number of secondary infectious persons resulting from one infectious person in the susceptible population. If the basic reproduction number is greater than 1, it describes the point where the epidemic starts. Fig. 3 illustrates the basic reproduction number equal to 5.

When introducing a national vaccination program, herd immunity can–theoretically at least–be reached, given the size of vaccine coverage. This coverage is set as a key target of the program and referred to as the herd immunity threshold (HIT). It is related to R_0 and can be calculated as follows:

$$\text{HIT} = 1 - \frac{1}{R_0} = \frac{R_0 - 1}{R_0}$$

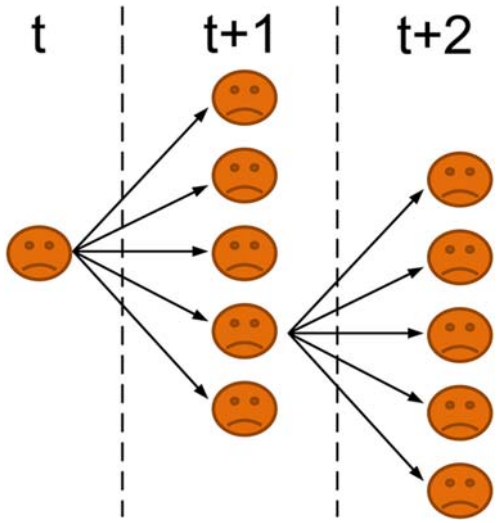

Fig. 3 An example of a disease where the basic reproduction number (R_0) is equal to 5 (adapted from Vynnycky, E. and White, R.G., 2010)[14].

Event rates

The event rate is the rate at which the population shifts between each compartment. In general, the rates are sometimes fixed. For example, the pre-infectious period is 2 days; therefore, the pre-infectious rate is equal to 0.5 per day. Therefore, setting the time step-size is very important as it will have an effect on the calculation, similar to setting the cycle length when using a Markov model. Infectious diseases usually have a small unit of time step-size, either in days or months unless they are for long-term infections. It is worth noting that the risk or the probability–the proportion of such event in each time step–should be used technically. However, the risk is approximately equal to the rate when the rate is small[14]. The relationship between rate and risk is shown as follows:

$$risk = 1 - e^{-rate}$$

Important elements that need to be considered when conducting an economic analysis of interventions for infectious diseases using a dynamic transmission model

Before using the number of infectious populations resulting from a dynamic model, the model needs to be validated through the use of local data such as the size of the infectious population at a given point in time. However, within developing countries, many epidemiological data like these are fragmented. Moreover, nationally-represented epidemiological data are sometimes collected passively from compulsory notifications and reporting from provincial hospitals and may require further tests to confirm the types of strains to which they refer. In addition, for some infections where hospitalization is not usually required, the data reported in the national surveillance may be understated. Active surveillance is, therefore, preferable. However, active surveillance usually requires additional resources that are often unavailable, and the data themselves may not be widely applicable, given that any information gathered may only be relevant to areas within which the samples have been collected.

An example of the limitations of available data can be seen with dengue fever in Thailand. The surveillance system in Thailand does not require laboratory confirmation to report dengue infection cases, and recent research revealed that passive surveillance is likely to underestimate incidence of dengue fever significantly when compared to rates revealed by active surveillance. Fig. 4 illustrates another example of the comparison between observed and predicted cases of influenza in Thailand; this example was chosen because national data are available.

Result presentation

When presenting results of economic evaluations of programs concerned with preventing or treating infectious diseases, researchers should ensure that all transmission dynamics, including the incidence or prevalence of the disease, should be reported over time. If the particular intervention or technology is able to cause herd immunity within the population, the effects of the technology should be presented separately as direct and indirect effects (see example in Fig. 5). Where applicable, the results should also outline any relevant information specific to the infectious disease, such as strain replacement or the development of drug resistance. A sensitivity analysis should also be conducted for important input parameters. For transparency, the initial values and the set of differential equations should be provided. For more information on appropriate results presentation, please refer to the guidelines of the ISPOR-SMDM Modeling Good Research Practices Task Force[7,8].

Although the demand for the use of dynamic transmission models in evaluations of health technologies for infectious disease is on the rise, they have not yet become part of the traditional toolbox of health economists, due in part to the fact that the results are complex and difficult to analyse, requiring extensive

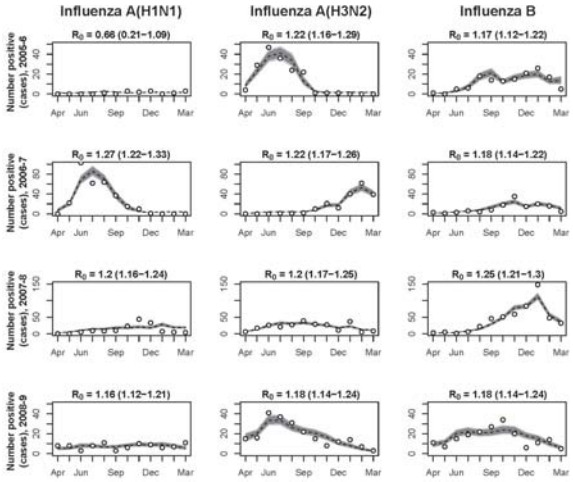

Fig. 4 An example of observed cases (dots) and predicted cases with 95% prediction intervals (shown via the dashed line and the shaded area, respectively) from the transmission model[15].

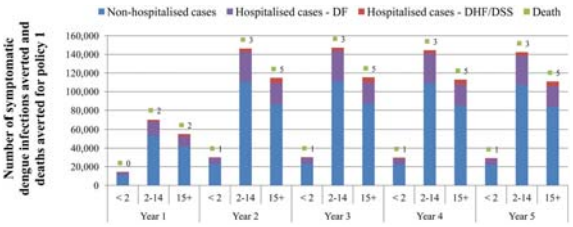

Fig. 5 An example of the predicted number of dengue cases averted, resulting from a hypothetical mass vaccination of dengue vaccine in children aged 2-14 years old (Policy 1). The direct effect of the vaccine is represented in the 2-14 age group, and the indirect effect is shown in the other age groups[16].

computational skills. Moreover, there may be times when researchers must present very complex data to non-technical decision-makers. In this case, while the comprehensibility of the data may be enhanced, the transparency of the analysis may be somewhat limited. Dynamic transmission modeling also requires numerous data, which may be a challenge, particularly in developing countries where good epidemiological data are not always available. In these cases, reasonable assumptions must be made, but this does allow the possibility of bias in the results.

Guidelines for Health Technology Assessment in Thailand (second edition): Recommendations for economic evaluation of infectious diseases

The most important step in evaluating technologies for infectious diseases is to understand whether a dynamic model is needed. For a dynamic model to be used in the economic evaluation, at least one of criteria below should be fulfilled:

1. The technology has an effect on the force of infection in the studied population.
2. The technology has an effect on the ecology of pathogen, such as strain replacement and antibacterial resistance.
3. The technology has an effect on the pathogenicity or the transmissibility of the disease, justified by the infection rate among other age groups.
4. The comparators of the interested technology have an impact on the infection rate.
5. There is a need for observing the incidence of the disease.

If none of the above criteria are met, a static model should be used. Moreover, a static model can also be used when existing studies with similar context show that certain technologies may represent good value-for-money. This is applicable for technologies known to have positive externalities, as the dynamic perspective will provide a more favourable incremental cost-effectiveness ratio.

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Potential conflicts of interest

None.

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แนวทางในการประเมินความคุ้มค่าด้านสุขภาพของโรคติดเชื้อ

ปฤษฐพร กิ่งแก้ว

ในปัจจุบันมีการนำเอาศาสตร์ด้านการสร้างตัวแบบเชิงคณิตศาสตร์หรือแบบจำลองคณิตศาสตร์เข้ามารวมกับการประเมินความคุ้มค่าทางสาธารณสุข มักพบได้มากในวรรณกรรมที่เป็นการประเมินความคุ้มค่าของวัคซีน การคัดกรองและการรักษาโรคติดเชื้อ ซึ่งเป็นการสร้างแบบจำลองไดนามิกทดแทนการสร้างแบบจำลองสถิติที่ใช้กันทั่วไป เช่น แบบจำลอง Markov และแบบจำลอง Decision tree เนื่องจากเทคโนโลยีที่ต้องการพิจารณานั้นส่งผลกระทบต่อการแพร่กระจาย ของเชื้อโรคทำให้อัตราการติดเชื้อในประชากรเปลี่ยนแปลงไป หรือส่งผลต่อนิเวศวิทยาของเชื้อโรค บทความนี้เป็นการทบทวนองค์ความรู้ในเบื้องต้นแก่ผู้ที่สนใจสร้างแบบจำลองไดนามิกโดยเน้นตัวอย่างของการประเมินความคุ้มค่าทางสาธารณสุขของวัคซีน พร้อมทั้งให้ข้อเสนอแนะสำหรับการประเมินความคุ้มค่าทางสาธารณสุขของโรคติดเชื้อ