The Reproduction Number of Hepatitis A in Thailand: a 10 Year-period Estimate Using the National Diseases Surveillance Data

Thapakorn Gonthongkum[*] *Prapassorn Pechgit*[**] *Kitiphong Harncharoen*[***]
Sopon Iamsirithaworn[****] *Aronrag Cooper Meeyai*[***]

ABSTRACT

The reproduction number, *R*, is the actual average number of secondary cases per primary case which is the useful information for understanding epidemic. If *R* exceeds 1, the epidemic is growing, while *R* less than 1, the epidemic decline or end. The cases of hepatitis A in the national disease surveillance from 2005 to 2014 were used to estimate the *R* by a likelihood-based estimation procedure and characterise the epidemic. The results showed that *R* of hepatitis A in Thailand are varied by provinces. An overall average *R* was 1.19 (95%CI=1.10-1.28). In endemic areas (low effective transmission), the *R* was 0.95 (95%CI=0.94-0.97). While in outbreak areas (high effective transmission), the *R* was 1.29 (95%CI=1.19-1.38). These findings suggest that the control measures for hepatitis A are highly required in the outbreak areas as soon as possible in order to control the transmission of hepatitis A viruses. However, estimation of *R* from epidemic curves can be underestimate as those asymptomatic infections were not included.

Keywords: reproduction number, hepatitis A, transmission, surveillance, Thailand

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Correspondence: Aronrag Cooper Meeyai. Department of Epidemiology, Faculty of Public Health, Mahidol University. Bangkok 10400, THAILAND. E-mail: a.meeyai@gmail.com

[*] Graduate student in Master of Science (Public Health) Program in Infectious Diseases and Epidemiology, Faculty of Public Health and Faculty of Graduate Studies, Mahidol University

[**] Department of Parasitology and Entomology, Faculty of Public Health, Mahidol University

[***] Department of Epidemiology, Faculty of Public Health, Mahidol University

[****] Department of Disease Control, Ministry of Public Health

Introduction

Hepatitis A is a liver inflammation caused by infection with hepatitis A virus (HAV)[1, 2] which is the most common cause of acute hepatitis symptom.[3] About 1.4 million people worldwide have HAV infection each year and tend to repeatedly occur due to a common-source outbreak, which related to consumption of contaminated food and water.[4] Such as in 2003 in the United State, there were 601 reported cases of hepatitis A who consumed contaminated green onions at a restaurant in Pennsylvania.[5] In 2013, an outbreak occurred in 11 European countries with approximately 1,300 reported cases of HAV due to consuming the contaminated frozen berries.[6]

In Thailand, hepatitis A is reported as an endemic disease[7]. The annual incidence is below 1 per 100,000 population in most years, except in 2005 and 2012 were 3.89 and 2.32 per 100,000 persons, respectively.[8] In 2005, a hepatitis A outbreak occurred in one district of Chiang Rai province with approximately 1,300 cases and distributed to a nearby district in the province and an adjacent district located in Lampang province with more than 500 cases reported in those areas.[9] In 2012, an outbreak of hepatitis A was reported in Bueng Kan province with approximately 1,200 cases.[10]

Understanding the transmissibility and virulence of hepatitis A would be useful for designing the most appropriate intervention or control strategies. There is a parameter based on the epidemic theory that can measure the potential transmission of an epidemic called the reproduction number (R) which is the actual average number of secondary cases per primary case at calendar time t, shows a time-dependent variation due to the decline in susceptible individuals and the implementation of control measures. If R exceeds 1 refers to the epidemic is growing and may be regarded as out of control at time, while R less than 1 refers to the epidemic is in decline and may be regarded as being under control.[11-13]

However, an estimation of the reproduction number of hepatitis A in Thailand has been limited. Due to many estimation methodologies for R require a complicated data, such as the number of susceptible, infection-age or incidence of infection. Wallinga and Teunis had developed methodology for estimation of the R which is only required the date of symptom onset routinely collected in the diseases surveillance.[13] This study applies that method to estimate the R of hepatitis A in Thailand.

Materials and Methods

Data Material

We used all the case of hepatitis A in Thailand during 2005 to 2014. There were obtained from the national disease surveillance center operated by the Bureau of Epidemiology, Department of Disease Control, Thailand Ministry of Public Health.[8] The cases of hepatitis A were defined based on the diagnostic criteria for public health surveillance as follows: a person who meets the clinical case definition and is laboratory confirmed hepatitis A or a person who meets the clinical case definition and occurs in a person who has an epidemiological link with a person who has laboratory-confirmed hepatitis A.[14]

Data analysis

The reproduction number (R) estimation

We estimated the daily *R* of hepatitis A by province using Wallinga and Teunis method which is a likelihood-based estimation procedure,[13] performed in R program. This method observed the date of symptom onset of the case for providing the epidemic curve and the probability distribution of the generation interval (τ) which is the time from symptom onset of the primary case (t_j) to symptom onset of the secondary case (t_i). The generation interval of hepatitis A was assumed to follow a gamma distribution with shape parameter 55.22 and scale parameter 0.50, corresponding to a mean 27.53 days and standard deviation 3.71 days of the hepatitis A infections.[15] The relative likelihood p_{ij} that case *i* has been infected by case *j*, given their difference in time of symptom onset t_i–t_j, expressed in terms of the probability distribution for the generation interval $w(\tau)$. The relative likelihood p_{ij} is the likelihood that case *i* has been infected by case *j* and normalized by the likelihood that case *i* has been infected by any other case *k*:

$$p_{ij} = w(t_i - t_j) / \sum_{i \neq k} w(t_i - t_k)$$

Thus, *R* for case *j* is the sum of all case *i* and weighted by the relative likelihood p_{ij}:

$$R_j = \sum_i p_{ij}$$

As this estimation method based on the likelihood inference for infection networks, the accuracy of the estimation relies on the assumption of transmission of infection (i.e. probability density function for the generation interval).

The R interpretation

The *R* exceeds 1 refers to the epidemic is growing and may be regarded as out of control at time, while *R* less than 1 refers to the epidemic is in decline and may be regarded as being under control.[11-13]

In addition, the daily *R* were used to calculate the annual average *R* for each

province from 2005 to 2014 and classified into 3 groups as follows; non-epidemic area (no case), endemic area ($0<R\leq1$), outbreak area ($R>1$).

Ethical statement

The study protocol (no.96/2560) complies with a research with exemption category was approved by the Standard Operating Procedures of Ethical Review Committee for Human Research, Faculty of Public Health, Mahidol University, Bangkok, Thailand.

Results

A total number of cases of hepatitis A during 2005-2014 were 7,497 cases (from 77 provinces). They were male 59.52% and female 40.48%. The mean of age was 28.98 years (S.D.=0.20). An overall average of *R* in Thailand was 1.19 (95%CI=1.10-1.28), means that each primary case produced approximately 1 secondary case. The annual average of *R* value highest in 2005 and 2012 was 1.78 (95%CI=1.35-2.22) and 1.45 (95%CI=0.93-1.97), respectively. Within study period, when classified the level of *R* found that, the most of provinces were located in an endemic area, the *R* was 0.95 (95%CI=0.94-0.97), and some provinces in the north and central regions tend to become a non-epidemic area (Figure 1). For outbreak area, we found 87 outbreaks (11.30%), the *R* was 1.29 (95%CI=1.19-1.38). The highest frequency outbreak occurred in 2012 (13 provinces) and lowest in 2014 (3 provinces) (Table 1). In particular, some provinces in the north and east regions are more likely to repeatedly outbreak every year (Figure 1).

For outbreak area group, two examples of the highest annual average of *R* value were Chiang Rai province 2005 (*R*=3.06) and Bueng Kan province in 2012 (*R*=3.32). Their epidemic curve indicated a common source outbreak (Figure 2A-2B). Chiang Rai province reported 1,272 cases, the first case occurred on 1 January 2005 and highest on 20 May 2005 with 119 cases. Bueng Kan province reported 1,066 cases, the first case occurred on 27 April 2012 and highest on 27 July 2012 with 116 cases. The value of *R* in both provinces is greater than 1 before the epidemic curve present the collection of cases. For example, *R* of Chiang Rai province was exceeded 1 at day 1 (1 January 2005), then slightly decreased and rise above 1 again at day 40 (9 February 2005) and peak at day 71 (12 March 2005) with maximum *R* value at 26.49 (Figure 2E). Meanwhile, the highest collection of cases illustrated by the epidemic curve of Chiang Rai province (Figure 2A) showed the peak of cases at day 140 (20 May 2005).

Table 1 The Total Number of Provinces in Categories (Non-epidemic Area, Endemic Area, Outbreak Area) of the Annual Average *R* of Hepatitis A in Thailand from 2005-2014. (N=77)

Year	Number of province (%)			Average reproduction number			
	Non-epidemic area (No case)	Endemic area (0<*R*≤1)	Outbreak area (*R*>1)	Mean	S.D.	Max	95%CI
2005	13 (16.88)	53 (68.83)	11 (14.29)	1.78	5.95	114.35	1.35, 2.22
2006	15 (19.48)	54 (70.13)	8 (10.39)	1.03	0.95	8.67	0.94, 1.12
2007	10 (12.99)	58 (75.32)	9 (11.69)	1.02	0.71	5.54	0.95, 1.10
2008	17 (22.08)	53 (68.83)	7 (9.09)	1.08	2.04	39.61	0.89, 1.28
2009	17 (22.08)	51 (66.23)	9 (11.69)	1.05	1.06	16.00	0.96, 1.15
2010	22 (28.57)	45 (58.44)	10 (12.99)	1.04	0.88	7.00	0.95, 1.12
2011	25 (32.47)	43 (55.84)	9 (11.69)	1.07	1.12	15.00	0.96, 1.17
2012	26 (33.77)	38 (49.35)	13 (16.88)	1.45	5.87	124.18	0.93, 1.97
2013	26 (33.77)	43 (55.84)	8 (10.39)	1.03	1.03	11.01	0.92, 1.13
2014	23 (29.87)	51 (66.23)	3 (3.90)	0.90	1.66	30.73	0.74, 1.05
Total	**198 (25.71)**	**485 (62.99)**	**87 (11.30)**	**1.19**	**3.24**	**124.18**	**1.10, 1.28**

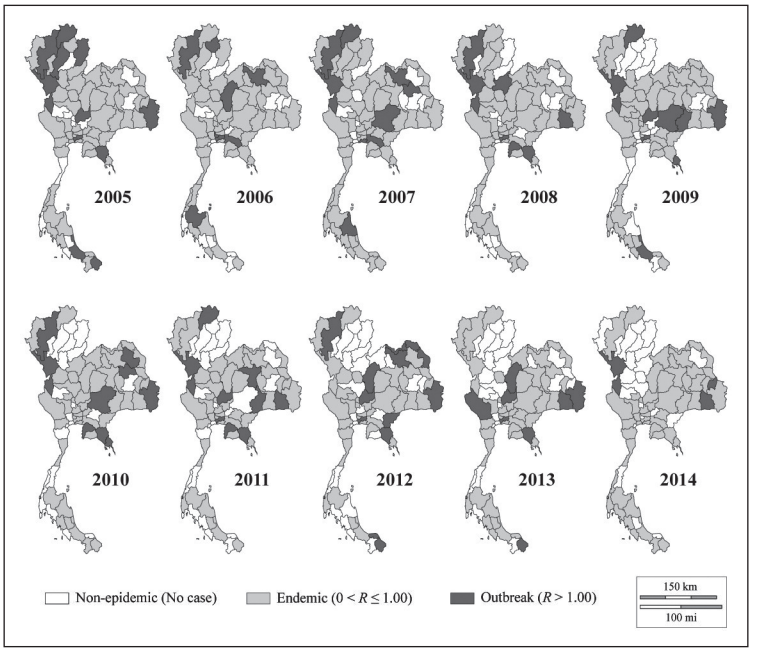

Figure 1 Geographical Distribution of the Annual Average *R* of Hepatitis A in Thailand from 2005 to 2014.

For endemic area, such as Tak and Chanthaburi provinces from 1 January 2005 to 31 December 2014 indicated sporadic cases throughout a 10-year period. Tak province reported 567 cases and the epidemic curve shows some outbreak, highest on 16 June 2008 with 5 cases (Figure 2C). For Chanthaburi province reported 201 cases and highest on 1 July 2005 with 2 cases (Figure 2D). The value of *R* was unstable with occasional outbreaks; an average of *R* was around 1 in both provinces. (Figure 2G-2H)

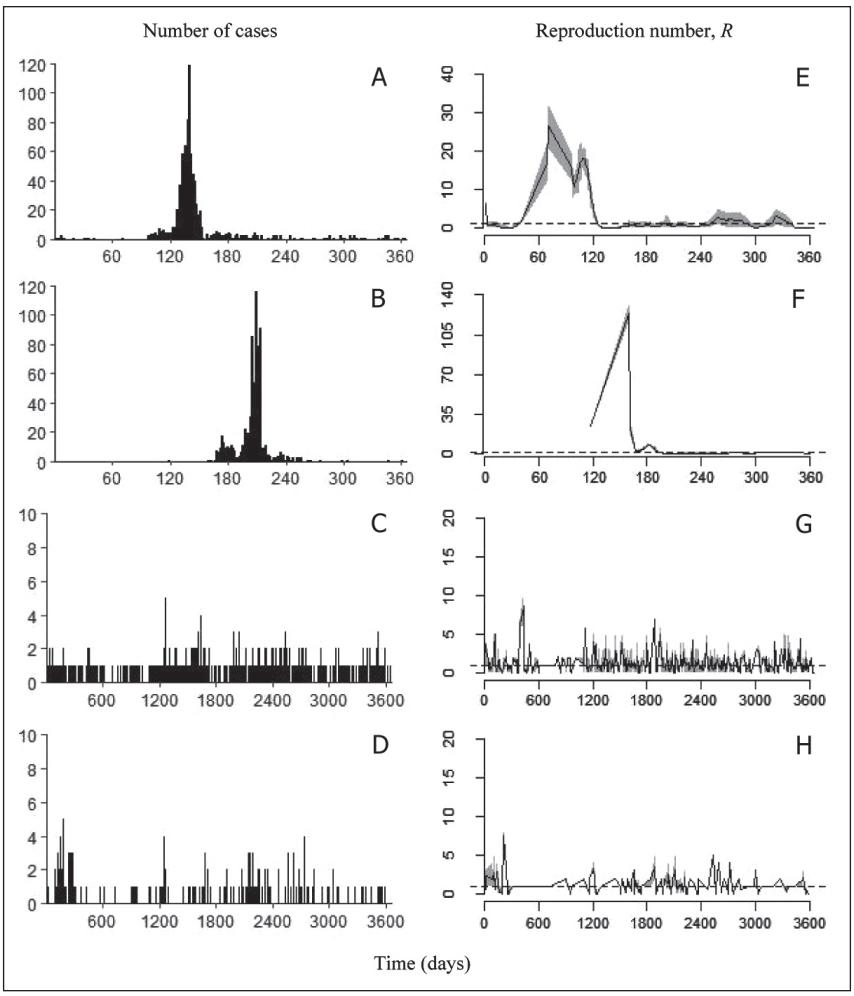

Figure 2 Epidemic Curve for Hepatitis A Outbreak in A) Chiang Rai 2005, B) Bueng Kan 2012 and Endemic in C) Tak 2005-2014, D) Chanthaburi 2005-2014. The *R* of Hepatitis A in E) Chiang Rai, F) Bueng Kan, G) Tak and H) Chanthaburi. In Graph E, F, G, and H, the Horizontal Dash Line Indicates the Value of *R* = 1 and Grey Band Show 95% Confidence Interval.

Discussion

The reproduction number of hepatitis A in Thailand varied by provinces and year. Hepatitis A in the most of provinces are low effective transmission with a small value of *R* was about 1, indicated that there are an endemic area. This result consisted with the classification by WHO, which classified Thailand as an intermediate endemicity of hepatitis A where is the most of population had been infected and have an immunity to HAV.[4, 7] In outbreak areas, a high value of *R* was estimated with the peak at 124.18. This indicated that HAV in some areas is high effective transmission due to a common-source outbreak. For example, Chiang Rai, Lampang, and Bueng Kan provinces reported that the cause of outbreak was a common-source due to consuming contaminated water.[9, 10] However, the cause of hepatitis A epidemic which repeatedly occurs may be an others potential transmission, due to hepatitis A have several routes of transmission, including food- and water-borne, sexual-contact, injection, or parenteral transmission.[2, 16] These components can be unraveled only when we obtain additional information.[13] Preventive measures of hepatitis A such as administration of hepatitis A vaccine to contact person with the case of hepatitis A in the outbreak setting as soon as possible are recommended.[17] In addition, there should be implemented together with improved personal hygiene such as hand-washing before and after meals or cooking, improve living standards, sanitation and environmental conditions such as improve drinking water supply and sanitary latrine.[2, 4]

Our study has some limitations. The cases of hepatitis A that had been reported in the national disease surveillance of Thailand, particularly in the outbreak, there may be included; suspected, probable and confirmed cases.[10] It would be over-estimate of *R* due to over-reported cases. While in endemic areas, the *R* may be under-estimated due to children are asymptomatic more than 80% and adults are symptomatic 75%[4] as demonstrated by the mean age of hepatitis A case in Thailand was 28.98 years; high proportion in the age group 11-20 year (25.70%), 21-30 year (19.27%), and 31-40 year (16.98%). Similar to the study of Seo JY. *et al.*[18] reported that hepatitis A in Korea from 2002-2012 frequently occurred in the age between 24-30 years. Thus, this results in *R* is more correctly represented in adults than children.[14] In addition, the estimated of *R* may be an ecological fallacy due to an estimation based on a provincial level. An outbreak of hepatitis A may not be occurring in all over the province, but there occurred in the limited areas in that province, such as district or village.

A further potential limitation is that the Wallinga and Teunis estimation model did not consider the route of transmission, susceptible population, and environmental factor (such as density of the pathogen) that is the main infectious components of infectious diseases.[19] Many researchers formulated the model to estimate the *R* that consists of difference component, for example; Nishiura and Chowell 11, Gay N.[20] and Keiding N.[21] estimated the *R* based on SIR model that consist of number of susceptible S, infection I, and recovered R to represent the transmission dynamic of the disease. While Clludia CT.[22] estimated the *R* of cholera which usually common-source outbreak, by added the concentration of pathogen and environmental factors into the model. For more appropriate model to estimate the *R* of hepatitis A should be based on SIR model together with environmental factors and asymptomatic rate. In addition, because HAV can be transmitted during the incubation period that before the symptoms appear. This estimation of *R* used the date of onset to observe the generation interval would not be appropriate for hepatitis A. For more accurate estimation, there should incorporate the generation interval of hepatitis A which is the time point of a primary case can be spread HAV, before symptoms appear. However, Wallinga and Teunis estimation model of *R* was likely to secondary attack rate, which is one kind of incidence that measured by the number of new cases among contacts of primary cases in an outbreak setting. There can be indicate the transmission of the diseases from the primary case same as the reproduction number and this method has required only the date of symptoms onset that is routinely collection and can be applied to routine surveillance.

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Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ค่าความเร็วการระบาดของโรคตับอักเสบเอในประเทศไทย: การประมาณค่าโดยใช้ข้อมูลการเฝ้าระวังโรคในช่วง 10 ปี

ฐาปกรณ์ ก้อนทองคำ[*] ประภัสสร เพ็ชรกิจ[**] กิติพงษ์ หาญเจริญ[***]
โสภณ เอี่ยมศิริถาวร[****] อรุณรักษ์ คูเปอร์ มีใย[***]

บทคัดย่อ

ค่าความเร็วการระบาด (Reproduction Number, *R*) คือ จำนวนเฉลี่ยของผู้ที่ติดเชื้อจากผู้ป่วยรายแรก ซึ่งเป็นข้อมูลที่มีประโยชน์อย่างมากที่จะช่วยให้เราเข้าใจถึงการระบาดของโรค ถ้าหากค่า *R* มีค่ามากกว่า 1 หมายความว่า มีการระบาด แต่หาก *R* มีค่าน้อยกว่า 1 หมายความว่าการระบาดลดลงหรือหมดไป การศึกษานี้ใช้ข้อมูลผู้ป่วยโรคตับอักเสบเอทุกรายจากรายงานการเฝ้าระวังโรคติดต่อตั้งแต่ปี พ.ศ.2548 ถึง พ.ศ.2557 เพื่อประมาณค่า *R* โดยใช้พื้นฐานของการประมาณความน่าจะเป็นและจำแนกการระบาดของโรคตับอักเสบเอ ผลการศึกษาพบว่า ค่า *R* ของโรคตับอักเสบเอของแต่ละจังหวัดนั้นมีความแตกต่างกัน ผู้ป่วยโรคตับอักเสบเอสามารถแพร่กระจายเชื้อทำให้เกิดผู้ป่วยเฉลี่ย 1 ราย (*R*=1.19, 95%CI=1.10-1.28) โดยพื้นที่ที่มีโรคตับอักเสบเอเป็นโรคประจำถิ่น (Endemic Area) จะมีความเร็วการระบาดต่ำ (*R*=0.95, 95%CI=0.94-0.97) ในขณะที่พื้นที่ระบาด (Outbreak Area) จะมีความเร็วการระบาดสูงกว่า (*R*=1.29, 95%CI=1.19-1.38) ข้อแนะนำจากการศึกษานี้คือ ควรมีการดำเนินมาตรการป้องกันควบคุมโรคตับอักเสบเอในพื้นที่ที่พบการระบาดให้เร็วที่สุดเท่าที่จะเป็นไปได้เพื่อควบคุมการแพร่ระบาดของเชื้อไวรัสตับอักเสบเอ อย่างไรก็ตามการประมาณค่า *R* จากเส้นโค้งการระบาด อาจได้ค่าต่ำกว่าความเป็นจริง เนื่องจากไม่ได้รวมผู้ป่วยที่ติดเชื้อแต่ไม่มีอาการในการประมาณค่า

คำสำคัญ: การระบาด, โรคตับอักเสบเอ, การเฝ้าระวังโรค, ประเทศไทย

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[*] นักศึกษาหลักสูตรวิทยาศาสตรมหาบัณฑิต (สาธารณสุขศาสตร์) สาขาโรคติดเชื้อและวิทยาการระบาดคณะสาธารณสุขศาสตร์ และบัณฑิตวิทยาลัย มหาวิทยาลัยมหิดล

[**] ภาควิชาปรสิตวิทยาและกีฏวิทยา คณะสาธารณสุขศาสตร์ มหาวิทยาลัยมหิดล

[***] ภาควิชาระบาดวิทยา คณะสาธารณสุขศาสตร์ มหาวิทยาลัยมหิดล

[****] กรมควบคุมโรค กระทรวงสาธารณสุข