Costs per DALYs Averted of Quadrivalent Influenza Vaccine versus Trivalent Influenza Vaccine in Elderly Population in Thailand

Jadesada Lertsirimunkong, Pharm.D.*, Wiwat Thavornwattanayong, M.A., Panasorn Hirunkanakorn, Pharm.D.**, Rujipas Buranapatanapong, Pharm.D.**, Sukanya Jermtienchai, Pharm.D.**, Nion Mingmoree, Pharm.D.****

**Department of Pharmacy Administration, College of Pharmacy, Rangsit University, Pathum Thani 12000, Thailand, **Department of Community Pharmacy, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand.*

ABSTRACT

Objective: Influenza is an infection of the respiratory system with a high annual incident rate. Influenza vaccine can reduce the severity of influenza and prevent transmission of the virus. Influenza vaccines in Thailand are the Trivalent Influenza Vaccine (TIV) and the Quadrivalent Influenza Vaccine (QIV). The cost and the effectiveness of the QIV in preventing transmission of the virus are greater than the TIV. Until now, no studies have been conducted to compare the economic impact of using QIV or TIV. This study aimed to evaluate the economic effects of using QIV versus TIV in Thai populations age 60 years and over.

Materials and Methods: The study was carried out from a societal perspective for cost per DALYs averted. A decision tree model was used to analyse the costs and DALYs averted of Thais after they received the vaccine.

Results: In a period of one year, it was found that in Thais age 60 years and over, the total cost of TIV was 2,445.19 baht with 0.0094 DALYs and total cost of the QIV was 2,629.28 baht with 0.0082 DALYs and the incremental cost-effectiveness ratio (ICER) of the QIV was 158,489.24 baht per DALYs averted. The acceptability curves demonstrated that the probability of QIV being cost-effective was 95% of the willingness to pay, being 1.2 times the Thai gross national income per capita.

Conclusion: Therefore, in Thai people age over 60 years and over, QIV is more cost-effective than TIV. The results of this study can be used by policymakers to help inform their decisions about which influenza vaccine is more cost-effective.

Keywords: Cost-effectiveness; DALYs averted; Influenza vaccine; Influenza; Trivalent Influenza Vaccine; Quadrivalent Influenza Vaccine (Siriraj Med J 2021; 73: 259-267)

INTRODUCTION

Influenza is a respiratory infection caused by the influenza virus.[1] There are three types of viruses that cause influenza in humans: A, B, and C. Influenza A has been a cause of worldwide pandemics (subtypes H1N1 and H3N2). Whereas influenza B has contributed to regional outbreaks only and influenza C is even less common.[1,2] Overall influenza occurs globally with an incidence rate of 5–10% in adults and 20–30% in children.[3]

Corresponding author: Jadesada Lertsirimunkong
E-mail: jadesada.l@rsu.ac.th
Received 23 December 2020 Revised 8 February 2021 Accepted 10 February 2021
ORCID ID: http://orcid.org/0000-0003-2930-8810
http://dx.doi.org/10.33192/Smj.2021.34

The World Health Organization (WHO) estimated that there are up to 650,000 deaths associated with influenza each year.[4] In Thailand in 2019, there were 390,733 cases with 27 leading to death. The mortality rate was 6.91 per 100,000 population.[5]

Vaccination is the most effective strategy to protect against influenza infection and to reduce its severity.[2] Each year WHO announces three virus strains that will be used in the manufacture for the trivalent influenza vaccine (TIV). Based on recommendations from WHO, Trivalent influenza vaccines contain two strains of A subtypes (H1N1 and H3N2) and one influenza B lineage from either the Yamagata or the Victoria lineage.[6,7] TIV effectiveness against A/H1N1 A/H3N2 and B/Yamagata lineage were 65%, 24%, and 49%[8], respectively. TIV needs to be evaluated annually to see whether its composition needs to be adjusted. This evaluation is based on the influenza strains that are expected to be in circulation during the upcoming influenza season. In Thailand from 2007 to 2012, there was a mismatch of 50% between the influenza B component of TIV and the result was a suboptimal vaccine. This mismatch led to the development of the Quadruple Influenza Vaccine (QIV). QIV contains two strains of influenza A and both B lineages (Yamagata and Victoria). QIV provides coverage and protection against the TIV-mismatched influenza B lineage.[9] Currently, the United States, Canada, Australia and the United Kingdom recommend QIV.[10] The efficacy of QIV (immune response) is 70% and TIV is 59%.[11,12] QIV would prevent influenza B 16% more than TIV.[11] These studies have shown that QIV is more effective than TIV.

From a systematic review, the influenza vaccine was not cost-effective in the population ages 18-59 years from a societal perspective.[13-15] So the influenza vaccination depends on each need. However some studies show the influenza vaccine was cost-effective in the population 60 years and over from a societal perspective.[16-25] The influenza vaccine is part of the health policy in Thailand and many other countries.[26,27] In Thailand, QIV is recommended as an alternative to TIV, but is more costly.[9] Also, hitherto now, a study had not been conducted comparing the cost-effectiveness of QIV and TIV. This study evaluated the cost-effectiveness between QIV and TIV from a societal perspective in Thai people ages 60 and over. Furthermore, the purpose of this study was to evaluate the economic outcomes between QIV and TIV and to develop a health policy for influenza vaccination.

MATERIALS AND METHODS

Study design

This study was a model-based economic evaluation in health technology assessment. A decision tree model was developed to compare the cost-effectiveness analysis from a societal perspective.

Intervention

There are 2 types of influenza vaccines in Thailand which are TIV and QIV. TIV includes influenza A (H1N1), influenza A (H3N2) and one lineage of influenza B which is based on recommendations from WHO, while QIV contains the same lineage as TIV and has another B lineage. The influenza vaccine is administered by an intramuscular injection of 0.5 ml once a year, due to the change in circulatory disseminated strains every year.

Decision Model

The decision tree model[28] was used to perform decision analysis. The study population was divided into two groups, those who received QIV and those who received TIV. Afterwards, when any of the population bacame infected by influenza and received treatment in a hospital, they were divided into an inpatient or an outpatient group, which had different levels of severity for symptoms and expenses. The model is presented in Fig 1 and was developed and validated by two experts with M.D. and Ph.D. degrees.

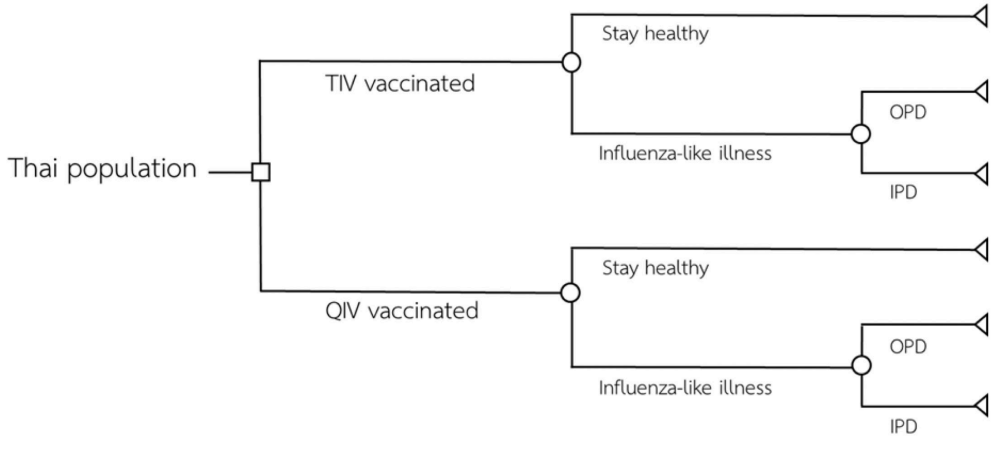

Fig 1. The decision tree model

Assumptions of the model

1. The study population is Thais ages 60 years and over.
2. The population in this model received the vaccination once a year.[29]
3. This model does not consider the occurrence of adverse reactions caused by receiving 3 species of TIV and 4 species of QIV.[29-32]
4. This model does not consider the very rare Guillain-Barré syndrome.[33]
5. This model does not consider the immunity.
6. The patients with symptoms of influenza infection received outpatient and inpatient treatment.
7. The coverage of influenza vaccination was 66%.[33]

Time Frame

The economic evaluation was considered by using a 1 year study framework to track the results of receiving TIV and QIV, since the influenza vaccine can prevent influenza in the first year of the outbreak.

Probability of clinical outcomes

A systematic search was conducted in PubMed, Cochrane Library, Scopus and Science Direct. The keywords were "Thailand", "Quadrivalent influenza vaccine", "Trivalent influenza vaccine" and "effectiveness". Two independent reviewers surveyed titles, abstracts, and articles based on the study eligibility criteria. The studies were identified as eligible for inclusion if they were published as full text and in the English language. All probabilities were obtained from the study which was included (i) randomized control trial, systematic review, or meta-analysis. If none of these were available an observational study was included instead and comprised (ii) a comparison of efficacy between QIV and TIV (iii) and injectable influenza vaccine (iv) through 2019. The studies were excluded if they met any of the following exclusion criteria: (i) non-English language and (ii) no full text. All probabilities are shown in Table 1.

Costs

All costs were expressed in Thai baht and are shown in Table 2. Cost of Quadrivalent Influenza Vaccine (per dose) was derived from the Hospital for Tropical Disease[34] and cost of TIV (per dose) was derived from the health technology assessment program.[33] All direct non-medical costs such as cost of transportation to the hospital, food, outpatient and inpatient treatment and productivity loss were obtained from the standard cost lists for health technology assessment in Thailand.[33]

All costs were adjusted to 2020 values using the consumer price index from the Bureau of Trade and Economic Indices, The Ministry of Commerce, Thailand.

Disability weight

Disability weight was used to measure outcomes. The humanistic outcomes were measured in disability weight for different health states after Thais received the vaccination. The average life expectancy in Thai people age 60 years and over was 14.49 years.[36] Disability weights were obtained from health technology assessment programme[33] and are shown in Table 3.

Sensitivity analysis

The one-way sensitivity analysis was performed by Microsoft Excel 2016. The parameter values were changed one by one, usually to a low and a high value. The results are presented by a tornado diagram. A Monte Carlo Simulation was used for probabilistic sensitivity analyses by Microsoft Excel 2016. All variables were randomized 1,000 times by probability distribution and the ICER estimated. The result is presented as a cost-effectiveness plane.

RESULTS

Cost-effectiveness analysis

The cost-effectiveness analysis was conducted from a societal perspective. It analysed the cost-effectiveness of the TIV and QIV vaccination in Thai population 60 years of age and over. The result shows that the total cost of TIV was 2,445.19 baht with 0.0094 DALYs while the total cost of the QIV was 2,629.28 baht with 0.0082 DALYs, and the incremental cost-effectiveness ratio (ICER) of the QIV was 158,489.24 baht per DALYs averted.

Sensitivity analysis

The one-way sensitivity analysis in Fig 2 was presented by a tornado diagram. The results showed that probability of illness from TIV was the variable with the most impact on the ICER.

The probabilistic sensitivity analysis in Fig 3 presented the incremental costs and DALYs averted for QIV compared with TIV as a cost-effectiveness plane. Each variable was randomized 1,000 times by the Monte Carlo simulations. The base-case ICER was presented in a yellow point and falls below the willingness to pay 160,000 baht. This revealed a probability of 95% that QIV was more cost-effective than TIV as shown in Fig 4.

TABLE 1. All parameters used in the decision tree model.

Probability parameters	Distribution	Mean	SE	References
Transitional probabilities				
Trivalent influenza vaccine (TIV)				
Probability of remaining healthy	Beta	0.5900	0.0408	Health Intervention and Technology Assessment Program[33]
Probability of changing health state from healthy to influenza infection	Beta	0.410	0.0408	Health Intervention and Technology Assessment Program[33]
Probability of changing health state from healthy to influenza infection with received an outpatient treatment	Beta	0.969	0.000172	Health Intervention and Technology Assessment Program[33]
Probability of changing health state from healthy to influenza infection with received an inpatient treatment	Beta	0.031	0.000172	Health Intervention and Technology Assessment Program[33]
Quadrivalent influenza vaccine (QIV)				
Probability of remaining healthy	Beta	0.616	0.0419	Health Intervention and Technology Assessment Program[33]
Probability of changing health state from healthy to influenza infection	Beta	0.394	0.0419	Health Intervention and Technology Assessment Program[33]
Probability of changing health state from healthy to influenza infection with received an outpatient treatment	Beta	0.970	0.000169	Health Intervention and Technology Assessment Program[33]
Probability of changing health state from healthy to influenza infection with received an inpatient treatment	Beta	0.030	0.000169	Health Intervention and Technology Assessment Program[33]

TABLE 2. Cost parameters used in the decision tree model.

Parameters	Distribution	Mean	SE	References
Cost parameters (baht)				
Cost of Trivalent influenza vaccine (per dose)	Gamma	208.08	20.81	Health Intervention and Technology Assessment Program[33]
Cost of Quadrivalent influenza vaccine (per dose)	Gamma	437.00	43.70	Hospital for tropical disease[34]
Vaccination fee (per dose)	Gamma	79.52	7.95	Health Intervention and Technology Assessment Program[35]
Cost of transportation to hospital (round-trip)	Gamma	209.52	20.95	Health Intervention and Technology Assessment Program[33]
Cost of food (per meal)	Gamma	36.34	3.63	Health Intervention and Technology Assessment Program[33]
Cost of productivity loss due to getting vaccination (per day)	Gamma	384.07	38.41	Health Intervention and Technology Assessment Program[33]
Cost of an outpatient treatment	Gamma	386.136	38.61	Health Intervention and Technology Assessment Program[33]
Cost of care giver's productivity loss (per day)	Gamma	384.07	38.41	Health Intervention and Technology Assessment Program[33]
Cost of an inpatient treatment	Gamma	9,221.71	922.17	Health Intervention and Technology Assessment Program[33]
Cost of care giver's food (per meal)	Gamma	36.34	3.63	Health Intervention and Technology Assessment Program[33]

TABLE 3. Disability weights used in the decision tree model.

Parameter	Distribution	Mean	SE	References
Health state				
Disability weight of symptomatic influenza infection	Beta	0.005	0.0018	Health Intervention and Technology Assessment Program[33]
Disability weight of influenza infection with out patient treatment	Beta	0.0078	0.0073	Health Intervention and Technology Assessment Program[33]
Diability weight of influenza infection with inpatient treatment	Beta	0.0217	0.0203	Health Intervention and Technology Assessment Program[33]

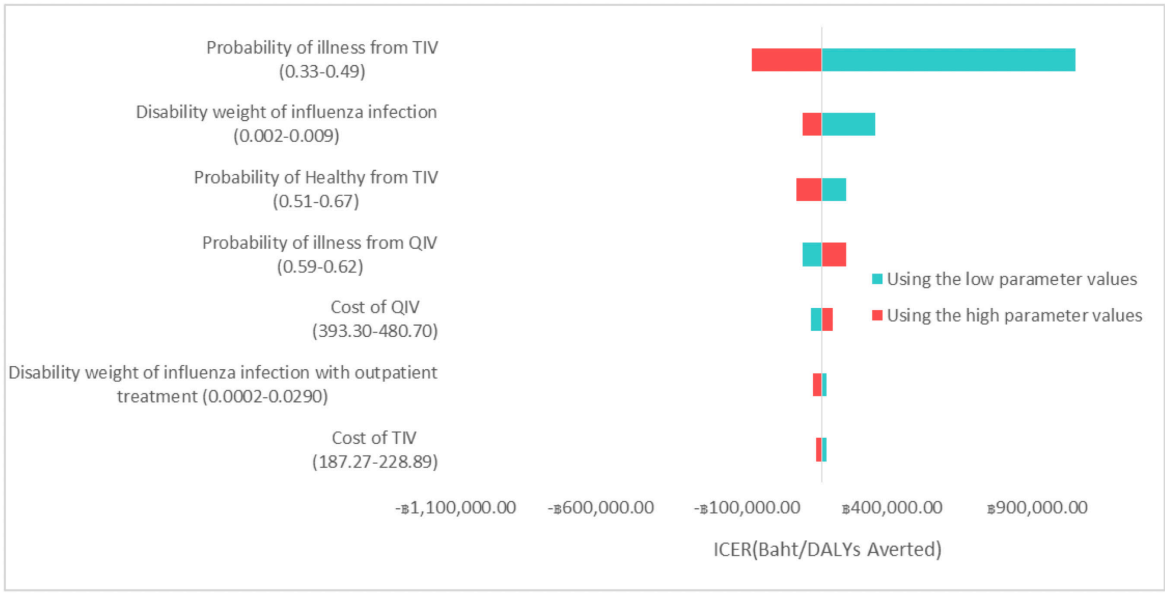

Fig 2. Tornado diagram showing the results of one-way sensitivity analysis

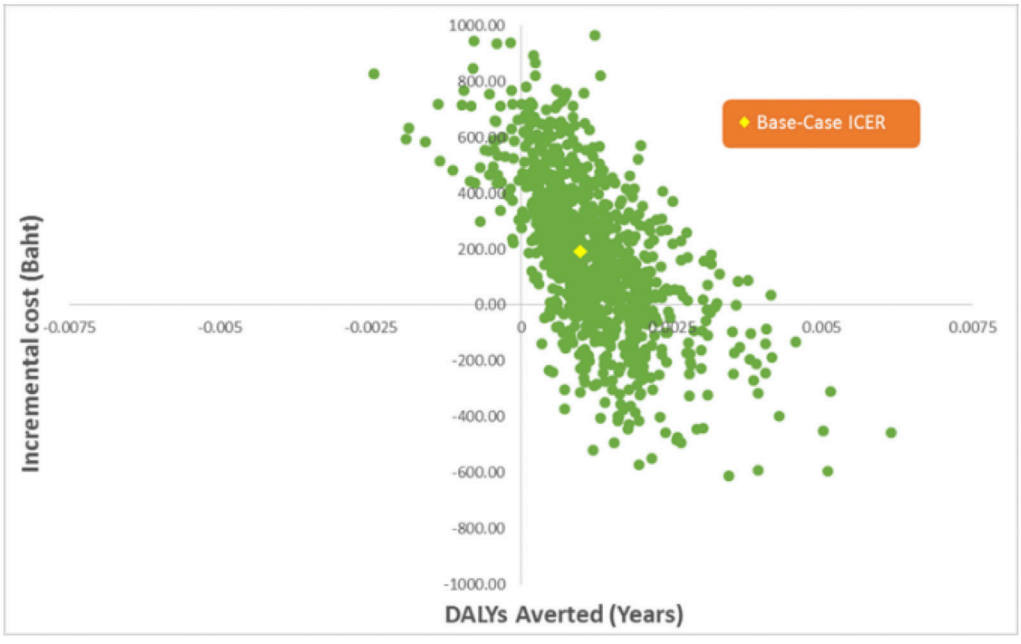

Fig 3. The cost-effectiveness plane between QIV and TIV

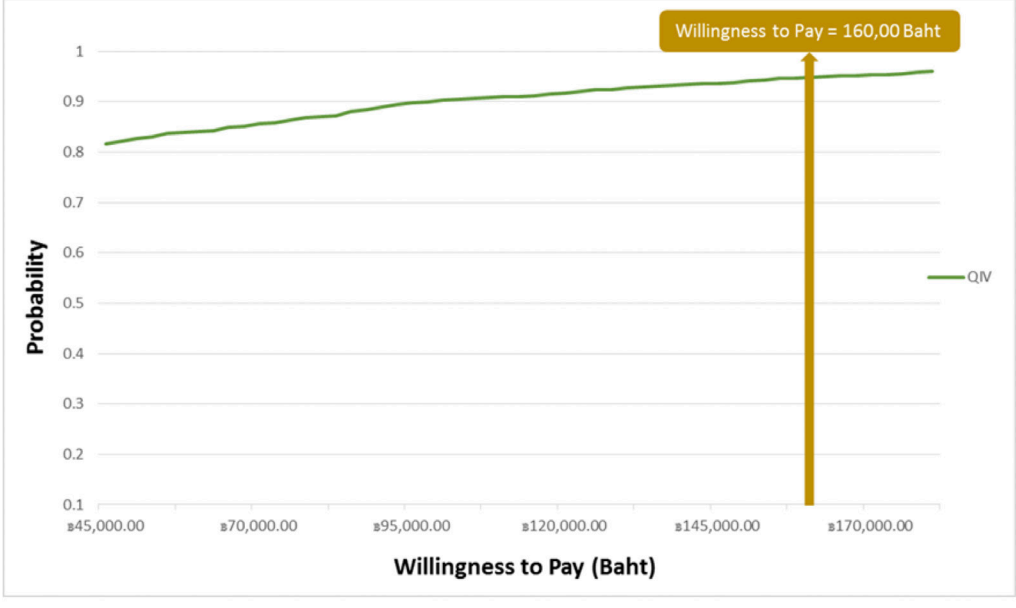

Fig 4. Acceptability curve

DISCUSSION

The cost effectiveness of the TIV and the QIV vaccination was analysed in this study. The study consists of a societal perspective, which was done in the Thai population 60 years and over. This cost effectiveness analysis was conducted to facilitate decision making regarding the selection of a vaccine. According to the Health Intervention and Technology Assessment Program (HITAP) recommendation of willingness to pay, the threshold for Thailand is 1.2 times of the gross national income (GNI) which equals 160,000 baht.[37] The results showed that QIV was more cost-effective than TIV with a probability of 95%.

Although TIV is a more attractive strategy for Thai's children, it has yet to be determined that this is so for Thai's elderly population.[7] Therefore, this study which used detailed accounting for the elderly on such metrics as life expectancy and cost, should help to clarify the current situation. This finding finds support from a corroboration of other results from previous studies from Finland[38], Germany[39] Vietnam[13] and China[40] that indicates the QIV is more cost-effective than the TIV.

According to the literature review, the effectiveness of QIV from studies in Italy, Canada, the USA, Taiwan, and Hong Kong were calculated from TIV.[41-46] Previous studies did not provide an effective report of the QIV in the Thais. However, similar analyses on the effectiveness of QIV data were collected from Kittikraisak W, et al.[9] and other studies from numerous countries. These data declare that the different rate of effectiveness between QIV and TIV is 0.16-4.6%.[9,17,41,43,47,48] However, vaccine effectiveness may be lower in Southeast Asia, and much lower in mass immunization campaign than in randomized trials.[49] In this study, the probabilistic sensitivity analysis (PSA) was done to reduce of an absence of reliable data.

Data was not only gathered on the effectiveness from many studies in years with and without an influenza epidemic, but also through the use of sensitivity analysis to predict the likelihood of an epidemic. Thus, this result may be used to consider annual vaccination in a year with and without an influenza epidemic. Limitations of this study but should not affect the conclusion. This study neglected mortality rate unrelated to influenza because it was analysed over a 1 year period only. Even though the study showed that influenza vaccination was less effective in the elderly who, at times, had to boost their dose or receive a double dose, some studies demonstrated that effectiveness did not improve.[50] Thus, this analysis did not focus on double doses or boosters. However, recent evidence reported that a high dose of influenza vaccination was more effective.[51] The analysis of the cost-effectiveness of a high-dose of TIV or QIV is recommended for further study.

This study is exempt from Human Ethics Committee (No. 60/2561) and did not receive any specific grant from funding agencies in the public or commercial domains.

CONCLUSION

Quadrivalent Influenza Vaccine is more cost-effective than Trivalent Influenza Vaccine in the prevention of influenza infection in the Thai population ages 60 years and over from a societal perspective. The results of this study could contribute to informed decision making by policymakers.

ACKNOWLEDGMENTS

We would like to thank Dr.John Tigue and Mr.Paul Mines, Faculty of Pharmacy Silpakorn University, for proofreading the article.

REFERENCES

1. Bureau of Epidemiology. Influenza [cited 2018 8 November]. Available from: http://www.boe.moph.go.th/fact/Influenza.htm.
2. World Health Organization. Influenza (Seasonal) [cited 2018 8 November]. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal).
3. World Health Organization. Vaccines against influenza. WHO position paper November 2012. 2012.
4. World Health Organization. Up to 650 000 people die of respiratory diseases linked to seasonal flu each year 2017 [cited 2018 8 November]. Available from: https://www.who.int/news-room/detail/14-12-2017-up-to-650-000-people-die-of-respiratory-diseases-linked-to-seasonal-flu-each-year.
5. Department of disease control. Department of disease control warns Thai people to beware influenza infection in this winter. 2020. Available from: https://ddc.moph.go.th/brc/news.php?news=10965&deptcode=brc&news_views=1382.
6. National Institute of Health of Thailand, Department of Medical Sciences, Ministry of Public Health, Thailand. Recommended composition of influenza virus vaccines for use in the 2018 southern hemisphere influenza season, 2017.
7. Meeyai A, Praditsitthikorn N, Kotirum S, Kulpeng W, Putthasri W, Cooper BS, et al. Seasonal Influenza Vaccination for Children inThailand: A Cost-Effectiveness Analysis. PLoS Med 2015;12: 1-25.
8. Flannery B, Chung JR, Belongia EA, McLean HQ, Gaglani M, Murthy K, et al. Interim Estimates of 2017–18 Seasonal Influenza Vaccine Effectiveness — United States, February 2018. MMWR Morb Mortal Wkly Rep 2018. 2018.p.180–5.
9. Kittikraisak W, Chittaganpitch M, Gregory CJ, Laosiritaworn Y, Thantithaveewat T, Dawood FS, et al. Assessment of potential public health impact of a quadrivalent inactivated influenza vaccine in Thailand. Influenza Other Resp 2016;10:211-9.
10. de Boer PT, van Maanen BM, Damm O, Ultsch B, Dolk FCK, Crépey P, et al. A systematic review of the health economic consequences of quadrivalent influenza vaccination. Expert

Rev Pharm Out 2017;17:249-65.
11. Tisa V, Barberis I, Faccio V, Paganino C, Trucchi C, Martini M, et al. Quadrivalent influenza vaccine: a new opportunity to reduce the influenza burden. J Prev Med Hyg 2016;57:E28-33.
12. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis 2012;12:36-44.
13. de Boer PT, Kelso JK, Halder N, Nguyen T-P-L, Moyes J, Cohen C, et al. The cost-effectiveness of trivalent and quadrivalent influenza vaccination in communities in South Africa, Vietnam and Australia. Vaccine 2018;36:997-1007.
14. Rothberg MB, Rose DN. Vaccination versus treatment of influenza in working adults: a cost-effectiveness analysis. Am J Med2005;118:68-77.
15. Bridges CB, Thompson WW, Meltzer MI, Reeve GR, Talamonti WJ, Cox NJ, et al. Effectiveness and cost-benefit of influenza vaccination of healthy working adults: A randomized controlled trial. JAMA 2000;284:1655-63.
16. Patterson BW, Khare RK, Courtney DM, Lee TA, Kyriacou DN. Cost-effectiveness of influenza vaccination of older adults in the ED setting. Am J Emerg Med 2012;30:1072-9.
17. Meier G, Gregg M, Poulsen Nautrup B. Cost-effectiveness analysis of quadrivalent influenza vaccination in at-risk adults and the elderly: an updated analysis in the U.K. J Med Econ 2015; 18:746-61.
18. Maciosek MV, Solberg LI, Coffield AB, Edwards NM, Goodman MJ. Influenza vaccination health impact and cost effectiveness among adults aged 50 to 64 and 65 and older. Am J Prev Med 2006;31:72-79.
19. Brydak L, Roiz J, Faivre P, Reygrobellet C. Implementing an Influenza Vaccination Programme for Adults Aged ≥ 65 Years in Poland. Clin Drug Invest 2012;32:73-85.
20. Shields GE, Elvidge J, Davies LM. A systematic review of economic evaluations of seasonal influenza vaccination for the elderly population in the European Union. BMJ Open 2017;7: e014847.
21. Baio G, Pammolli F, Baldo V, Trivello R. Object-oriented influence diagram for cost-effectiveness analysis of influenza vaccination in the Italian elderly population. Expert Rev Pharmacoecon Outcomes Res 2006;6:293-301.
22. Lugnér AK, van Boven M, de Vries R, Postma MJ, Wallinga J. Cost effectiveness of vaccination against pandemic influenza in European countries: mathematical modelling analysis. Brit Med J 2012;345:e4445.
23. Postma MJ, Bos JM, van Gennep M, Jager JC, Baltussen R, Sprenger MJ. Economic evaluation of influenza vaccination. Assessment for The Netherlands. Pharmacoeconomics 1999;16 Suppl 1:33-40.
24. Scuffham PA, West PA. Economic evaluation of strategies for the control and management of influenza in Europe. Vaccine 2002;20:2562-78.
25. Department of Epidemiology and Department of International health policy development Moph, Thailand. Cost-effectiveness of influenza vaccine in population age over 60 years and over with chronic diseases in Thailand in 2008, 2011.
26. Centers for Disease Control and Prevention. International Influenza Report FY 2016–2017. Atlanta: US Department of Health and Human Services.
27. National Health Security Office (NHSO) T. Influenza vaccination in high risk population 2018. Available from: https://www.nhso.go.th/frontend/NewsInformationDetail.aspx?newsid=MjM0NQ==.
28. Dilokthornsakul P, Chaiyakunapruk N. Decision analysis model I: Decision tree model. Center for Continuing Pharmaceutical Education, 2016.p.1-16.
29. Infectious Disease Association of Thailand. Recommended Adult and Elderly Immunization Schedule 2018. Available from: https://www.idthai.org/Contents/Views/?d=qwzJ!17!4!!390!fb86LuPe.
30. Greenberg DP, Robertson CA, Noss MJ, Blatter MM, Biedenbender R, Decker MD. Safety and immunogenicity of a quadrivalent inactivated influenza vaccine compared to licensed trivalent inactivated influenza vaccines in adults. Vaccine 2013;31:770-6.
31. Song JY, Lee J, Woo HJ, Wie SH, Lee JS, Kim SW, et al. Immunogenicity and safety of an egg-based inactivated quadrivalent influenza vaccine (GC3110A) versus two inactivated trivalent influenza vaccines with alternate B strains: A phase III randomized clinical trial in adults. Hum Vaccin Immunother 2019;15:710-6.
32. Trombetta CM, Gianchecchi E, Montomoli E. Influenza vaccines: Evaluation of the safety profile. Hum Vaccin Immunother 2018;14:657-70.
33. Health Intervention and Technology Assessment Program (HITAP), Department of Health, Ministry of Public Health. Cost-utility analysis of seasonal influenza vaccine among school children in Thailand, 2013.
34. Hospital for Tropical Diseases. Vaccine Price List 2020. Available from: https://www.thaitravelclinic.com/th/cost-th.html.
35. Health Intervention and Technology Assessment Program (HITAP). Standard Cost List For Health Technology Assessment 2009. Available from: http://costingmenu.hitap.net/.
36. Health Information System Development Office. Life Expectancy of Thai population. Available from: https://www.hiso.or.th/hiso/visualize/Index.php?links=v1.
37. The Subcommittee of National List of Essential Medicines Development. The Manual of Health Technology Assessment in Thailand Volume 2. Nonthaburi, Thailand: Watcharin Printing Co., Ltd, 2013.
38. Nagy L, Heikkinen T, Sackeyfio A, Pitman R. The Clinical Impact and Cost Effectiveness of Quadrivalent Versus Trivalent Influenza Vaccination in Finland. Pharmacoeconomics 2016;34:939-51.
39. Dolk C, Eichner M, Welte R, Anastassopoulou A, Van Bellinghen LA, Poulsen Nautrup B, et al. Cost-Utility of Quadrivalent Versus Trivalent Influenza Vaccine in Germany, Using an Individual-Based Dynamic Transmission Model. Pharmacoeconomics 2016;34: 1299-308.
40. Jiang M, Li P, Wang W, Zhao M, Atif N, Zhu S, et al. Cost-effectiveness of quadrivalent versus trivalent influenza vaccine for elderly population in China. Vaccine 2020;38:1057-64.
41. Capri S, Barbieri M, de Waure C, Boccalini S, Panatto D. Cost-effectiveness analysis of different seasonal influenza vaccines in the elderly Italian population. Hum Vaccin Immunother 2018; 14:1331-41.
42. Mennini FS, Bini C, Marcellusi A, Rinaldi A, Franco E. Cost-effectiveness of switching from trivalent to quadrivalent inactivated influenza vaccines for the at-risk population in Italy. Hum Vaccin Immunother 2018;14:1867-73.
43. Thommes EW, Ismaila A, Chit A, Meier G, Bauch CT. Cost-effectiveness evaluation of quadrivalent influenza vaccines for seasonal influenza prevention: a dynamic modeling study of Canada and the United Kingdom. Bmc Infect Dis 2015;15:465.

44. de Boer PT, Crépey P, Pitman RJ, Macabeo B, Chit A, Postma MJ. Cost-Effectiveness of Quadrivalent versus Trivalent Influenza Vaccine in the United States. Value Health 2016;19:964-75.
45. Yang MC, Tan EC, Su JJ. Cost-effectiveness analysis of quadrivalent versus trivalent influenza vaccine in Taiwan: A lifetime multi-cohort model. Hum Vaccin Immunother 2017;13:81-9.
46. You JH, Ming WK, Chan PK. Cost-effectiveness of quadrivalent influenza vaccine in Hong Kong - A decision analysis. Hum Vaccin Immunother 2015;11:564-71.
47. Chit A, Roiz J, Briquet B, Greenberg DP. Expected cost effectiveness of high-dose trivalent influenza vaccine in US seniors. Vaccine 2015;33:734-41.
48. Van Bellinghen LA, Meier G, Van Vlaenderen I. The potential cost-effectiveness of quadrivalent versus trivalent influenza vaccine in elderly people and clinical risk groups in the UK: a lifetime multi-cohort model. PloS One 2014;9:e98437.
49. Russell CA, Jones TC, Barr IG, Cox NJ, Garten RJ, Gregory V, et al. The global circulation of seasonal influenza A (H3N2) viruses. Science 2008;320:340-6.
50. Roos-Van Eijndhoven DG, Cools HJ, Westendorp RG, Ten Cate-Hoek AJ, Knook DL, Remarque EJ. Randomized controlled trial of seroresponses to double dose and booster influenza vaccination in frail elderly subjects. J Med Virol 2001;63:293-8.
51. Saade E, Canaday DH, Davidson HE, Han LF, Gravenstein S. Chapter 3 - Special Considerations for Vaccines and the Elderly. In: Poland GA, editor. Vaccinations: Elsevier; 2019.p.35-53.