HHS Public Access

Author manuscript

Br J Dermatol. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

Br J Dermatol. 2017 October ; 177(4): 1102–1112. doi:10.1111/bjd.15498.

Is Universal *HLA-B*15:02* Screening a Cost-Effective Option in an Ethnically-Diverse Population? A Case Study of Malaysia

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Abstract

Background—Strong association was documented between human leukocyte antigen (*HLA)-B*15:02* and carbamazepine-induced severe cutaneous adverse reactions (SCARs) in Asians. Beyond Asia, the *HLA* testing is potentially valuable in many countries with increasingly diverse communities of Asian ancestry, to facilitate an early recognition of patient susceptibility to SCARs.

Objective—To determine the cost-effectiveness of universal *HLA-B*15:02* screening in preventing carbamazepine-induced Stevens-Johnson syndrome/ toxic epidermal necrolysis in an ethnically-diverse Malaysian population.

Methods—A hybrid model of a decision tree and Markov model was developed to evaluate three strategies for treating newly-diagnosed epilepsy among adults - (i) carbamazepine initiation without *HLA-B*15:02* screening (current practice); (ii) universal *HLA-B*15:02* screening prior to carbamazepine initiation; and (iii) alternative treatment [sodium valproate (VPA)] prescribing without *HLA-B*15:02* screening. From a societal perspective, base-case analysis and sensitivity analyses were performed over lifetime time horizon. Incremental cost-effectiveness ratios were calculated.

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Conflict of Interest Disclosures: All authors declare no conflict of interest.

Results—In the base-case analysis, both universal *HLA-B*15:02* screening and VPA prescribing were dominated by current practice. Compared to current practice, universal *HLA-B*15:02* screening resulted in 0.0255 quality-adjusted life years (QALYs) loss at an additional cost of USD707, while VPA prescribing resulted in 0.2622 QALYs loss at an additional cost of USD4,127, due to estimated differences in antiepileptic treatment efficacy.

Conclusions—This study suggests that universal *HLA-B*15:02* screening is unlikely to be a cost-effective intervention in Malaysia compared to current practice. However, with the emergence of an ethnically-diverse population in many other countries, this may render *HLA-B*15:02* screening a potentially viable intervention when an increasing proportion of the population is at risk and an equally effective yet safer antiepileptic drug is available.

Introduction

Severe cutaneous adverse reactions (SCARs), predominantly represented by Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)[1] are the most severe, life-threatening idiosyncratic reactions. Although rare, SCARs impose significant public health impact because of high mortality and morbidity.[2-4] More importantly, 30-70% of surviving patients suffer from SJS/TEN sequelae that could last a lifetime.[4-6]

Medication use is related to 80% of SCAR cases.[3] Among a wide spectrum of medications reported to be causal in SCARs,[7-9] carbamazepine (CBZ) is the most highly investigated cause of SJS/TEN.[10] Substantial evidence revealed the strong association between *HLA-B*15:02* and CBZ-induced SJS/TEN in Asians [overall odds ratio (OR) 80, 95% confidence interval (CI) 28-224].[11] This has led to the adoption of mandatory human leukocyte antigen (*HLA*) testing in several Asian countries.[12] Furthermore, this testing is potentially valuable beyond Asia given the increasingly diverse communities with Asian ancestry in many countries, for example, a 56% growth in the Asian population was reported in the US between 2000 to 2013,[13] leading to the recommendation of *HLA-B*15:02* screening for all patients of Asian descent prior to CBZ treatment by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and US Food and Drug Administration (FDA).[14,15] Thus, it is important to ensure such test is made available to facilitate an early recognition of patient susceptibility to SCAR among these widely-distributed *HLA-B*15:02* carriers.

With the rising trend of modern immigration worldwide, leading to increased ethnic diversity in many countries, it is fundamental to incorporate this differential SCARs susceptibility among ethnicities in an ethnically-diverse population for better understanding of the cost-effectiveness of this HLA testing to support an informed decision making. Using the example of Malaysia, which features uniquely as a multi-ethnic country, this study aimed to determine the cost-effectiveness of universal *HLA-B*15:02* screening prior to CBZ initiation in an ethnically-diverse population.

Methods

The human research ethics approval was granted by the institutional review boards of the University of Malaya Medical Centre (UMMC) (reference number: 1135.15) and Monash University (reference number: CF15/2497 – 2015001009).

Model Structure

A hybrid model consisting of a decision tree and a Markov model was adapted from a previous study[16,17] to project the cost and health outcomes of three treatment strategies to prevent CBZ-induced SJS/TEN. The model began with a decision tree emulating different treatment strategies (Figure 1). All patients subsequently encountered two possible outcomes at the end of the decision tree – (1) the development of SJS/TEN and (2) no development of SJS/TEN. A Markov model with a 1-year cycle length was developed to estimate the lifetime effects of each outcome. In those who developed SJS/TEN, they may either have recovered with/without sequelae and be treated with an alternative antiepileptic drug (AED), or have died, while those who did not develop SJS/TEN continued to be treated with AED and may either be in remission, have uncontrolled epilepsy, or have died (Figure 2A and 2B).

As recommended by the Malaysian Pharmacoeconomics Guideline,[18] the base-case analysis was performed using the societal perspective over a lifetime time horizon. Utilities and costs were assigned to each clinical event and health state in annual cycles, and discounted at 3% annually. The analyses were performed using Microsoft Excel® (Microsoft Corp., Redmond, WA).

Target Population

The modeled population consisted of a hypothetical cohort of newly-diagnosed epilepsy Malaysian adults aged 19 years old, in whom CBZ was considered suitable as first-line monotherapy, considering that the average age of epilepsy onset was 19 years old among Malaysian adults.[19]

Treatment Strategies

Three treatment strategies were modeled – (1) current practice: CBZ initiation without *HLA-B*15:02* screening, (2) universal *HLA-B*15:02* screening before CBZ initiation, and (3) alternative AED – sodium valproate (VPA) prescribing without *HLA-B*15:02* screening.

To reflect current practice, all newly-diagnosed epilepsy adult patients received CBZ treatment.[20] In the universal screening strategy, patients underwent *HLA-B*15:02* testing before CBZ initiation. Those who tested *HLA-B*15:02* positive received VPA,[20] while those with negative *HLA-B*15:02* received CBZ. In the third treatment strategy, VPA was prescribed, thus eliminating the need for a *HLA-B*15:02* screening.

The alternative AEDs included VPA for patients who developed CBZ-induced SJS/TEN and for patients in whom CBZ treatment failed, while topiramate (TPM) for patients who developed VPA-induced SJS/TEN and for patients in whom VPA treatment failed. Although no-or-very low SJS/TEN risks have been reported for VPA[7,21] and TPM,[21] evidence suggests that VPA and TPM may not be as efficacious as CBZ, with 13% and 16% fewer patients achieving 12-month remission associated with VPA [Hazard ratio (HR) 0.87; 95%CI 0.74-1.02][22] and TPM (HR 0.84; 95%CI 0.70-1.01),[23] respectively were reported. The differential efficacy and safety of AEDs were reflected in our model through annual

probabilities of remission and treatment failure due to inadequate seizure control and unacceptable adverse events and were assumed constant after year 6.[24]

Generally, epilepsy patients have increased mortality risk compared to the general population,[25-29] reflected by a 42% increase in mortality [Standardized mortality ratio (SMR) 1.42; 95%CI 1.16–1.72] for newly-diagnosed epilepsy patients and a two-fold increase in mortality (SMR 2.05; 95%CI 1.83–2.26) for uncontrolled epilepsy patients.[30] It was assumed that there is no increased risk among patients who were in remission.[30]

Lifelong epilepsy treatment was assumed as there is limited evidence that supports AED withdrawal in seizure-free adults[31] due to the higher-than-average risk of seizure relapse associated with adult-onset epilepsy and partial seizures.[32]

Predictive Value of HLA-B*15:02 Genotyping

An ethnicity-weighted prevalence of *HLA-B*15:02* carriers in Malaysia was estimated to be 15% (95%CI 13%-18%) based on a meta-analysis of the respective allele frequency among the three major ethnicities – Malay, Chinese, and Indian (Appendix 1).[33-36]

The ethnicity-specific incidence of CBZ-induced SJS/TEN was assumed to be similar to Singapore[37] due to the historical similarities. The ethnicity-weighted incidence of CBZ-induced SJS/TEN for the general population in Malaysia was estimated to be 0.46%. Using the association between *HLA-B*15:02* and CBZ-induced SJS/TEN in the Malaysian population (OR 221; 95%CI 4-12,695),[11] the probabilities of CBZ-induced SJS/TEN in patients with and without *HLA-B*15:02* were calculated to be 2.95% and 0.01%, respectively (Appendix 2).

We assumed that the probability of VPA-induced SJS/TEN was similar to CBZ-induced SJS/TEN in patients who were *HLA-B*15:02* negative, while a zero-probability of TPM-induced SJS/TEN was assumed, as evidence suggests that the incidence of VPA-induced SJS/TEN ranges from 0[21] to 0.5 per 10,000,[7] and no SJS/TEN cases reported for TPM.[7]

Costs and Utilities

From the societal perspective, costs included were (i) direct medical costs – *HLA-B*15:02* test, epilepsy treatment, SJS/TEN event, and sequelae treatment, (ii) direct non-medical costs – transportation and additional food expenditure, and (iii) indirect costs – productivity loss due to illness (Table 1). The costs were converted to 2015 Malaysian Ringgit (MYR) and US dollar (USD) using the consumer price index[38] and exchange rate.[39]

A bottom-up, micro-costing was employed to determine the cost of a SJS/TEN event. Based on the resource utilization data collected from 19 patients diagnosed with SJS/TEN and hospitalized in UMMC from 1 January 2013 to 31 December 2014 (4 were CBZ-induced) and institution-specific cost data, the average cost of a SJS/TEN event was MYR7,729 (USD1,876) using a non-parametric bootstrap method with 10,000 resampling.

For the cost of epilepsy management, it was assumed that patients had 3 specialist visits per year, with constant drug costs throughout treatment. The annual cost of epilepsy treatment

was estimated to be MYR982 (USD238) with CBZ, MYR1,000 (USD243) with VPA, and MYR5,581 (USD1,355) with TPM.

Since severe dry-eye syndrome (DES) was the most common late ocular complication of SJS/TEN,[6,40] the annual cost of DES treatment was estimated to be MYR554 (USD135) (Table 1).

Direct non-medical costs comprised transportation costs and additional food expenditure incurred by patient and/or a caregiver during hospital visits for SJS/TEN, and clinic visits for epilepsy and DES. These were calculated based on government-approved rates and a national survey.[41,42]

Indirect cost was estimated based on daily productivity loss derived using age-specific mean daily wage[43] and the number of days loss due to illness – 1 day for follow-up, and average length of hospital stay for a SJS/TEN event in this study.

The utility of each health state was derived for the quality-adjusted life year (QALY) estimation based on patient interviews using the EQ-5D-3L questionnaire[44] or published literature.[16,45] The utility of SJS/TEN elicited from patient interviews was derived from a Malaysian EQ-5D tariff.[46] Since there was no data for utility of epilepsy patients with DES, we estimated this utility using the multiplicative approach by Ara et al.[47]

Main Outcome Measures

The primary outcome was the incremental cost-effectiveness ratio (ICER; incremental cost per QALY gained) for universal *HLA-B*15:02* screening or VPA prescribing versus current practice over the lifetime analytic horizon. Secondary outcome was the number of patients who would need to be screened (NNS) to avert one SJS/TEN event.

Base-case Analysis

Using the societal perspective, we calculated the expected costs and outcomes of three proposed treatment strategies among patients with newly diagnosed epilepsy aged 19 years old for whom CBZ was considered suitable as first-line monotherapy. Results were presented as an ICER for universal *HLA-B*15:02* screening or VPA prescribing versus current practice.

A cost-effectiveness threshold of 1 time of gross domestic product per capita [≈MYR37,000 (USD8,982)][48] was used to determine the optimal strategy in base-case and sensitivity analyses.[49,50]

Sensitivity Analyses

To determine the robustness of the estimates from the base-case analysis, several sensitivity analyses were performed. A series of one-way sensitivity analyses were performed to investigate the effects of altering each parameter within the plausible ranges (Table 1). In addition, a probabilistic sensitivity analysis (PSA) was employed to assess the simultaneous impact of parameter uncertainties using a Monte Carlo simulation with 1,000 replicates of parameters sampled from the assigned distributions (Table 1). A cost-effectiveness

acceptability curve was generated to illustrate the probability of each strategy being cost-effective for a given willingness-to-pay (WTP) threshold.[51]

A threshold analysis was performed to determine the critical value of the probability of CBZ-induced SJS/TEN in *HLA-B*15:02* positive patient which drives universal *HLA-B*15:02* screening to be cost-effective at the WTP threshold of MYR37,000 (USD8,982) per QALY.

A scenario analysis was performed to examine the robustness of cost-effectiveness findings when the Malaysia Ministry of Health (MOH) fee schedule for foreigners[52] was used in the direct medical costs estimation in our model. This was assumed to represent the actual costs of the services including all administrative costs, professional fees and relevant costs incurred in the provision of medical services.

Results

Base-case Analysis

In base-case analysis, both universal *HLA-B*15:02* screening and VPA prescribing were dominated by current practice. Compared to current practice, universal *HLA-B*15:02* screening resulted in 0.0255 QALYs loss at an additional cost of MYR2,912 (USD707), while VPA prescribing resulted in 0.2622 QALYs loss at an additional cost of MYR17,002 (USD4,127) (Table 2). As for seizure control, the highest number of patients with 12-month remission was estimated in current practice (n=847), followed by universal *HLA-B*15:02* screening (n=833), and VPA prescribing (n=740).

In the universal *HLA-B*15:02* screening and VPA prescribing, there was 1 SJS/TEN per 10,000 patients, compared to 46 in current practice. The NNS to prevent one SJS/TEN event is 222.

Sensitivity Analyses

Tornado plots in Figure 3, 4 respectively illustrate the sensitivity of the incremental costs and incremental QALYs to the 10 most influential parameters in the universal *HLA-B*15:02* screening and VPA prescribing when compared to current practice. It was demonstrated that the hazard ratio of efficacy associated with VPA had the greatest potential impact on both incremental costs and incremental QALYs. Another parameter that significantly influenced the incremental costs was discount rate of cost, while the key driver of the incremental QALYs was the probability of CBZ-induced SJS/TEN in *HLA-B*15:02* positive patients. The PSA revealed that, at the WTP threshold of MYR37,000 (USD8,982) per QALY, current practice was cost-effective in 96% of simulations (Figure 5).

Compared to current practice, the threshold analysis suggested that the ICER of universal *HLA-B*15:02* would fall below the WTP threshold when the probability of CBZ-induced SJS/TEN in *HLA-B*1502* positive patients increased from 2.95% to 15.40%.

When the MOH fee schedule for foreigners was used for direct medical cost estimation, the ICER findings remained unchanged with modest reduction in the incremental costs for both

universal *HLA-B*15:02* screening and VPA prescribing. Similar PSA findings were obtained where current practice was cost-effective in 93% of simulations at the WTP threshold (Appendix 3).

Discussion

This economic evaluation of treatment strategies to prevent CBZ-induced SJS/TEN in adult epilepsy patients demonstrates that the use of either universal *HLA-B*15:02* screening or VPA prescribing is likely to lead to worse clinical and economic outcomes compared to current practice. Although both treatment strategies reduced the incidence of CBZ-induced SJS/TEN, both strategies were more costly and less effective than current practice. This information is of use to healthcare policy and decision-makers when placing the position of universal *HLA-B*15:02* screening in Malaysia.

The cost-effectiveness findings were attributed to the reduced clinical efficacy of alternative AEDs, leading to poorer seizure management, thus resulted in overall QALY loss. Given the low positive predictive value of the *HLA-B*15:02* genotyping (2.95%), 15.3% of patients who test positive would be switched to an alternative AED - VPA in this case whereas only 2.95% of them would developed SJS/TEN if treated with CBZ. As a result, the QALY gained from SJS/TEN averted could not offset the QALY loss from the suboptimal seizure control with VPA in the universal *HLA-B*15:02* screening approach. For VPA prescribing, all patients were worse off, as indicated by the larger QALY loss. Despite the relative lack of cost difference between CBZ and VPA, which was unique to Malaysia, our findings are somewhat generalizable to other countries. In a situation where larger drug cost difference exists, VPA prescribing would likely to be a more unfavourable strategy due to the higher cost incurred.

The findings of universal *HLA-B*15:02* screening being dominated were robust in a series of sensitivity analyses. In the one-way sensitivity analyses, varying these variables in our model did not alter the cost-effectiveness results. Furthermore, the PSA showed that universal *HLA-B*15:02* screening had only a 4% probability of being cost-effective at the MYR37,000 (USD8,982) per QALY threshold. Although increased probability of CBZ-induced SJS/TEN in *HLA-B*15:02* positive patients had a substantial impact on the incremental QALY, the overall cost-effectiveness findings remain unchanged due to the low likelihood of a 5-fold increase from 2.95% to 15.4% in the probability of CBZ-induced SJS/TEN in *HLA-B*15:02* positive patients, in order for universal *HLA-B*15:02* screening to be cost-effective in Malaysia.

Contrary to previous published cost-effectiveness studies in Thailand[16] and Singapore,[37] our model incorporated several additional aspects to improve the validity of this analysis. Firstly, the long-term differential impacts of AEDs on seizure control and other adverse drug reactions (ADRs) were taken into account. In addition, a systematic review of economic evaluations of pharmacogenetic testing for ADR prevention highlighted the unrealistic scenario of an alternative drug having zero-ADR incidence in these economic evaluations which would lead to a bias towards pharmacogenetic testing.[53] This is in convergence with our findings which were sensitive to both variations in seizure remission and treatment

failure rates between AEDs. This implied that the assumption of similar efficacy and zero-incidence of other ADRs among AEDs was potentially misleading. Secondly, a lifelong AED treatment was modeled in our study, which would be representative of real-world clinical practice based on the current evidence base.[31,32]

A few limitations of the study deserve discussion. The choice of alternative AEDs modeled was confined to VPA and TPM only. Although phenytoin may deem to be a better substitute, a meta-analysis confirmed a clinically relevant association between the *HLA-B*15:02* allele and phenytoin-induced SJS/TEN.[54] Therefore, VPA and TPM were selected on the basis of the low incidence rates of SJS/TEN reported based on their monotherapy use.[7,21] Moreover, the paucity of evidence related to comparative efficacy among AEDs deterred newer AEDs to be included for comparison. It is also important to note that the choice of alternative AED may differ in other countries, thus an understanding of the local alternative AED is essential for accurate modelling. In addition, the full spectrum of long-term SJS/TEN sequelae was not captured. Despite several severe complications of SJS/TEN having been documented,[55] the evidence remains scanty. Thus, an accurate estimate could not be derived with the current evidence, potentially leading to an underestimation of the SJS/TEN sequelae cost. Amniotic membrane transplant, an emerging treatment for severe ocular manifestations of SJS/TEN,[56,57] is yet to be adopted in Malaysia, so this was not considered in the model.

Beyond Asia, our study in an ethnically-diverse population may provide a useful cost-effectiveness template for other countries due to the rapidly changing landscape of racial and ethnic compositions worldwide. In comparison to other cost-effectiveness findings of *HLA-B*15:02*, it is highly suggestive that its economic value is dependent on the ethnic composition in the country and their associated SCAR susceptibility. Notably, in the US, it is forecasted that no racial or ethnic group will constitute a majority of the population within 4 decades, while Asians are projected to be the largest immigration group by 2055.[54] Through modern immigration, a substantial proportion of the US population is potentially at risk of *HLA-B*15:02*-related SJS/TEN, thus giving rise to the need to determine the cost-effectiveness of a universal *HLA-B*15:02* screening even in a Caucasian-dominant country. In addition, it is important to address the intrinsic equity issue when conducting economic evaluations particularly those involving genetic testing. If an economic evaluation of genetic testing has been undertaken based on a dominant ethnic in the country, the findings may fall short in determining the value of genetic testing for a society as a whole. By considering the variation of SCAR susceptibility among different ethnicities in an economic evaluation, its findings would have embedded the element of equity, leading to an informed and equitable decision-making.

Based on the best available evidence, universal *HLA-B*15:02* screening is unlikely to be a clinically and economically-attractive preventive strategy compared to current practice, mainly driven by the reduced efficacy of alternative AED. In addition, it is important to recognize that cost-effective information must be considered with a variety of other factors, e.g. ethical, social issues to inform health policy development.

Conclusion

From a cost-effectiveness standpoint, this study suggests that universal *HLA-B*15:02* screening is unlikely to be a cost-effective intervention in Malaysia compared to current practice. This information can be used along with other factors to assist policy makers in efficiently allocating limited resources. At a broader perspective, with the emergence of an ethnically-diverse population in many countries of the world due to modern immigration, this may render *HLA-B*15:02* screening a possible intervention when the proportion of the population at risk is increasing and an equally effective yet safer AED for *HLA-B*15:02* carriers is available at an acceptable cost.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Yin Yen Wong (UMMC Pharmacy Department) for drug cost data sharing; Professor Dr. Chong Tin Tan (UMMC Neurology Department), Associate Professor Dr. Nurliza Khaliddin (UMMC Ophthalmology Department), and Associate Professor Dr. Alizan Abdul Khalil (UM Surgical Department, Faculty of Medicine) for their expert opinion. The authors are grateful to Associate Professor Dr. Usa Chaikledkaew and Dr. Surakameth Mahadirimongkol for the economic model sharing and training; Dr Dyson Wake from University of Florida for sharing literature searches conducted.

Funding: This study is funded by the US National Human Genome Research Institute (research grant number U01 HG007269).

Role of the Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

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What's already known about this topic?

- The *HLA-B*15:02* allele is strongly associated with carbamazepine (CBZ)-induced Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) in Asians, thus the adoption of mandatory *HLA-B*15:02* testing in several Asian countries.
- Beyond Asia, this testing is potentially valuable due to the increased ethnic diversity driven by modern immigration in many countries. This leads to an increasing proportion of the population is at risk even in Caucasian-dominant countries.

What does this study add?

- Our study in an ethnically-diverse population may provide a useful cost-effectiveness template for others to facilitate an evidence-informed decision-making.
- Although universal *HLA-B*15:02* screening reduced the CBZ-induced SJS/TEN incidence, it was more costly and less effective than current practice.
- Given the emergence of an ethnically-diverse population in many countries, this may render *HLA-B*15:02* screening a possible intervention when the at-risk-proportion of the population is increasing and an equally effective, safer antiepileptic drug for *HLA-B*15:02* carriers is available at an acceptable cost.

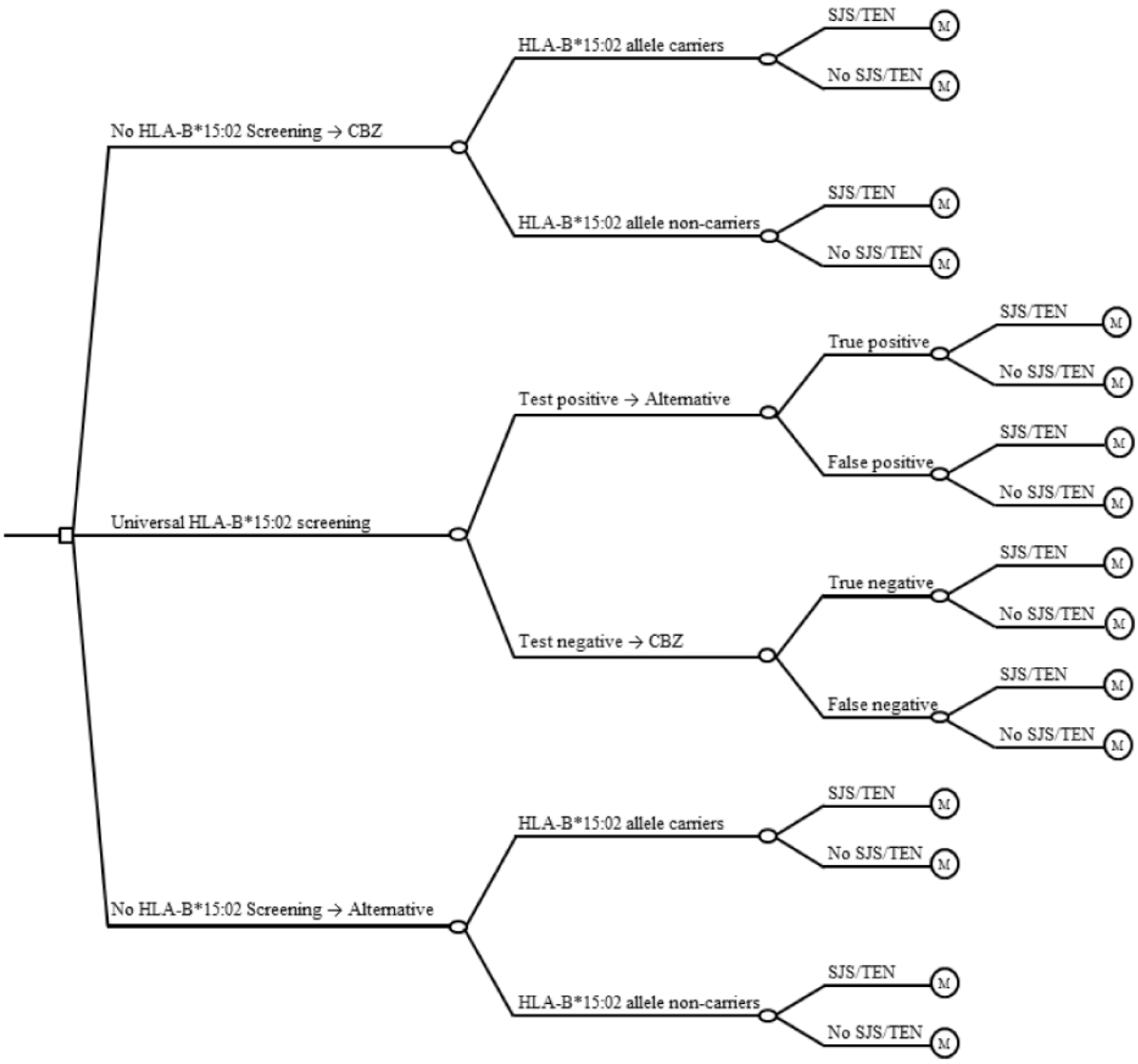

Figure 1.

Decision tree model. Patients with newly-diagnosed epilepsy will receive three different treatment strategies.

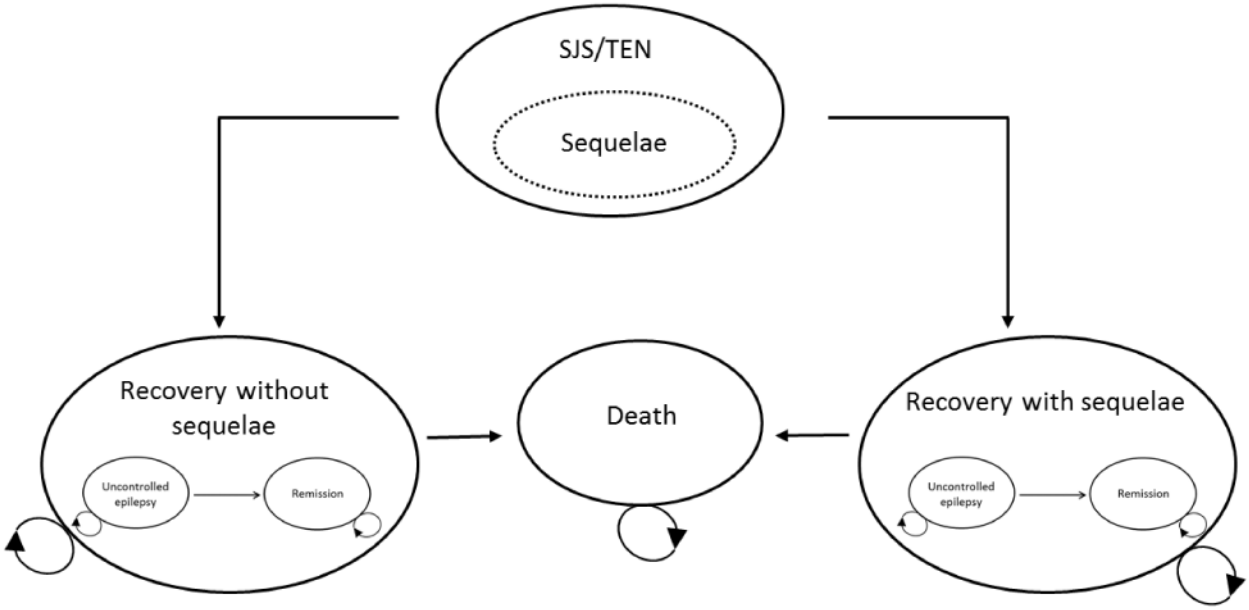

Figure 2A.

Markov model I. Patients who developed SJS/TEN after receiving drug will enter this Markov model from the decision tree model.

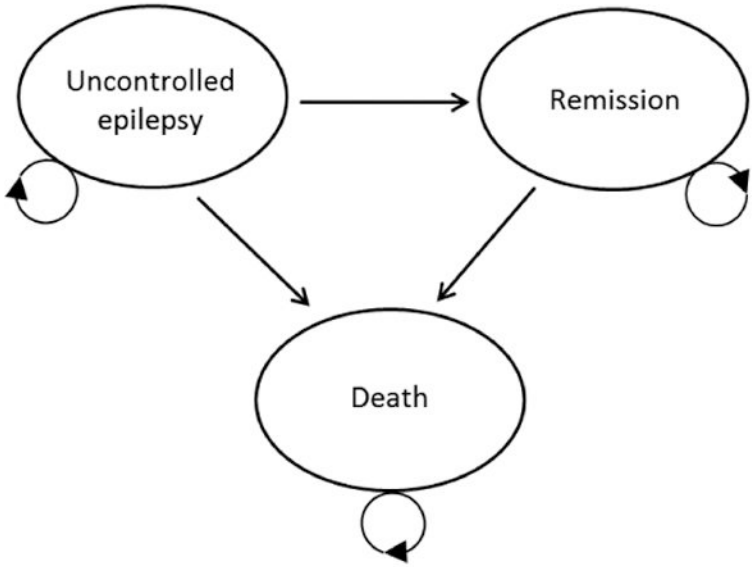

Figure 2B.

Markov model II. Patients who did not developed SJS/TEN and were treated AED will enter this Markov model from the decision tree. It was assumed that no transitions from the remission state to that of uncontrolled epilepsy.

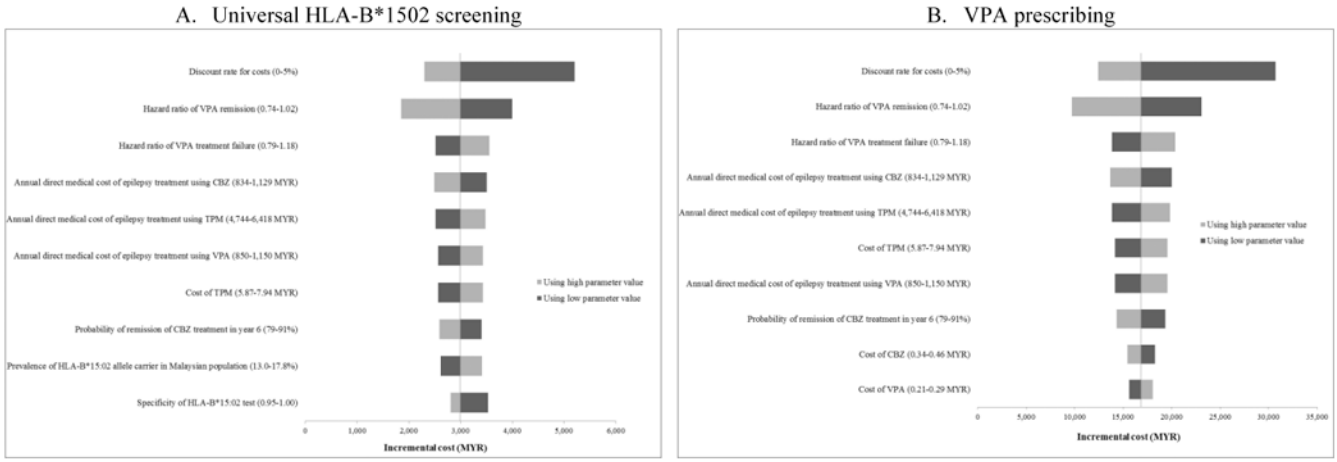

Figure 3.

Tornado plot represents the univariate influence of key parameters in the incremental cost between (A) universal *HLA-B*15:02* screening versus current practice, and (B) VPA prescribing versus current practice. The horizon bars represent the range of ICER over the range of parameters in parenthesis. The wider the horizon bar, the more uncertainty that parameter introduces. The vertical line represents the base-case ICER.

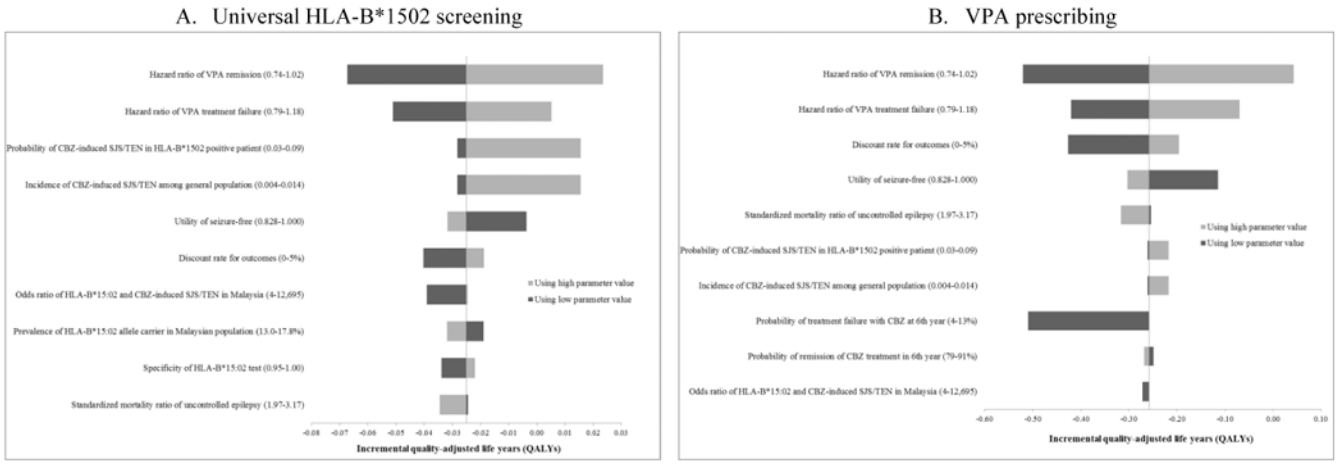

Figure 4.

Tornado plot represents the univariate influence of key parameters in the incremental QALYs between (A) universal *HLA-B*15:02* screening versus current practice, and (B) VPA prescribing versus current practice. The horizon bars represent the range of ICER over the range of parameters in parenthesis. The wider the horizon bar, the more uncertainty that parameter introduces. The vertical line represents the base-case ICER.

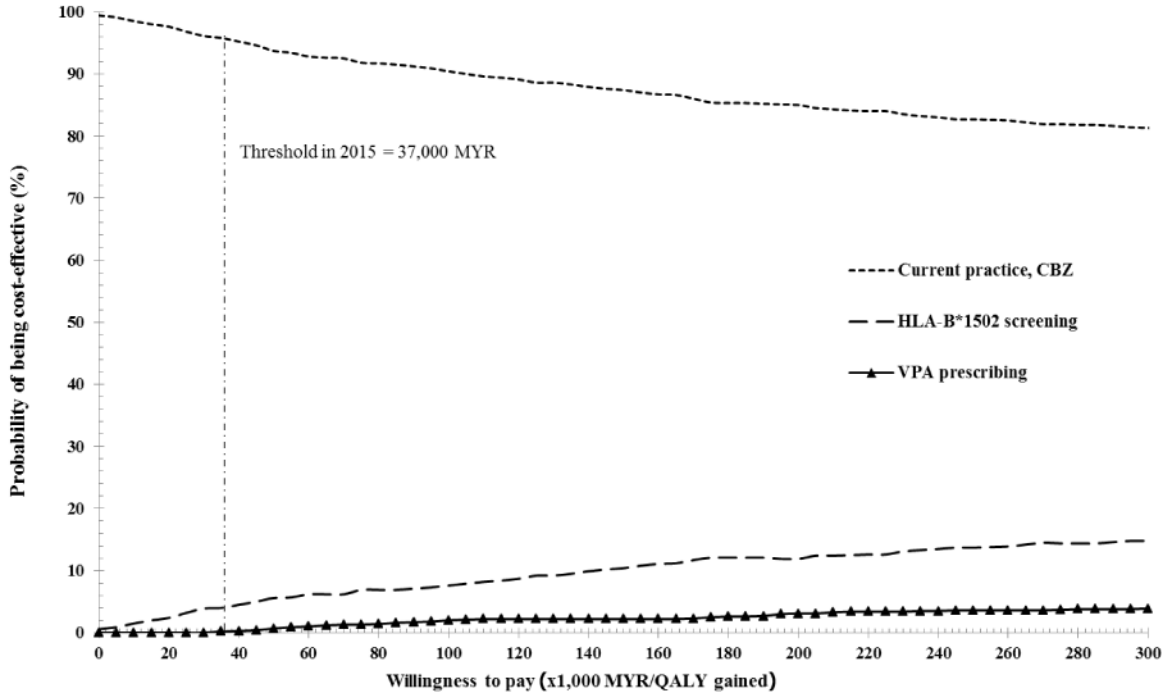

Figure 5.

Cost-effectiveness acceptability curves of 3 treatment strategies generated from the Monte Carlo simulation in probabilistic sensitivity analysis. The vertical line indicates the WTP threshold at which current practice is cost effective for 96% simulations.

Table 1
Key input parameters, values and data sources used in the model

Parameters	Base case	Range	Source(s)
Epidemiological data			
Prevalence of *HLA-B*15:02* carrier	0.153	0.129-0.178	33-35 *a*
Test characteristics			
Sensitivity	1.000	0.950-1.000	58
Specificity	0.987	0.950-1.000	58
Probabilities			
Probability of CBZ-induced SJS/TEN, %			
General population	0.463	0-1.369	37
*Patients with HLA-B*15:02 positive*	2.951	2.508-8.735	Calculated *b*
*Patients with HLA-B*15:02 negative*	0.013	0.0114-0.0154	Calculated *b*
Probability of patients developing ocular sequelae	0.406	0.341-0.470	6,40
Probability of death among CBZ-induced SJS/TEN	0.042	0-0.120	59
Hazard ratio of remission			
VPA	0.87	0.74-1.02	22
TPM	0.84	0.70-1.01	23
Hazard ratio of treatment failure			
VPA	0.97	0.79-1.18	22
TPM	1.13	0.93-1.37	23
Standardized mortality ratio			
Newly-diagnosed epilepsy	1.42	1.20-1.66	30
Uncontrolled epilepsy	2.06	1.97-3.17	30
Remission	1.00	NA	30
Gene-disease association			
Association of *HLA-B*15:02* and CBZ-induced SJS/TEN in Malaysian population	221.00	3.85-12,694.65	11
Costs (2015 USD) *c*			
Direct medical care costs			
*HLA-B*15:02* genetic screening	59.34	13.05-82.72	58
Epilepsy treatment (per year)			
CBZ	238.39	202.58-274.07	Calculated *d*
VPA	242.76	206.34-279.17	Calculated *d*
TPM	1,354.78	1,151.56-1,557.99	Calculated *d*
SJS/TEN treatment (per event)	1,876.27	1,379.80-2,501.41	UMMC *e,f*
Follow-up of DES (per year)	134.52	114.34-154.69	45
Direct non-medical care costs			
Transportation (per visit)			
Clinic	2.41	2.05-2.77	Calculated *g*
Hospital	6.03	5.13-6.94	Calculated *g*

Parameters	Base case	Range	Source(s)
Additional food cost (per person per visit)	2.55	2.17-2.93	Calculated[h]
Indirect costs (daily productivity loss by age)			
Age 15-19 years	7.57	NA	[43]
Age 20-24 years	10.86	NA	[43]
Age 25-29 years	15.37	NA	[43]
Age 30-34 years	18.91	NA	[43]
Age 35-39 years	21.05	NA	[43]
Age 40-44 years	23.50	NA	[43]
Age 45-49 years	25.51	NA	[43]
Age 50-54 years	26.33	NA	[43]
Age 55-59 years	28.58	NA	[43]
Age 60-64 years	18.64	NA	[43]
Utilities (EQ-5D)			
Epilepsy	0.69	0.68-0.70	[16]
Seizure-free	0.96	0.83-1.00	[37]
SJS/TEN	0.29	0.20-0.36	UMMC[e,f]
DES	0.68	0.57-0.79	[45]

Notes

[a] Calculated based on the ethnicity distribution in Malaysia using ethnic-specific allele frequency resulted from meta-analysis.

[b] Calculated using the probability of CBZ-induced SJS/TEN in general population.

[c] Converted at the rate of USD1=MYR4.12[39]

[d] Included annual specialist visits, laboratory tests, and drugs.

[e] Calculated from primary data collected in UMMC.

[f] Analysis of primary data using bootstrap method.

[g] Calculated by multiplying total distance to healthcare facility (8.7km/way for clinic visit, while 21.8km/way for hospital visit)[42] and standard transportation rate per km.[41]

[h] Calculated from the average MOH claims per meal.

Abbreviations: CBZ, carbamazepine; DES, dry-eye syndrome; EQ-5D, European Quality of Life-5 Dimensions; HLA, human leukocyte antigen; MOH, Ministry of Health; NA, not applicable; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; UMMC, University Malaya Medical Center.

Table 2

Results of base-case analysis[i]

Strategy	Cost (MYR/ USD[j])	Effectiveness (QALYs)	Incremental cost (ΔMYR/ΔUSD[j])	Incremental effectiveness (ΔQALYs)	ICER (ΔMYR/ΔQALYs)
Current practice	31,643/7,682	22.44			
Universal *HLA-B*15:02* screening	34,555/8,389	22.41	2,912/707	-0.0255	Dominated[k]
VPA prescribing	48,645/11,809	21.18	17,002/4,127	-0.2622	Dominated[k]

Notes

[i]Discounted at 3% per year

[j]Converted at the rate of USD1=MYR4.12[39]

[k]The treatment strategy incurred more costs but resulted in lower QALYs than that of current practice

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; VPA, sodium valproate.

Table 3

Results of scenario analysis[l]

Strategy	Cost (MYR/USD[m])	Effectiveness (QALYs)	Incremental cost (ΔMYR/ΔUSD[m])	Incremental effectiveness (ΔQALYs)	ICER (ΔMYR/ΔQALYs)
Current practice	36,744/8,920	22.44			
Universal *HLA-B*15:02* screening	38,856/9,433	22.41	2,648/643	-0.0255	Dominated[n]
VPA prescribing	51,516/12,506	21.18	15,307/3,716	-0.2622	Dominated[n]

Notes

[l] Discounted at 3% per year

[m] Converted at the rate of USD1=MYR4.12[39]

[n] The treatment strategy incurred more costs but resulted in lower QALYs than that of current practice

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; VPA, sodium valproate.