

REVIEW



Landscape of vaccine access and health technology assessment role in decision-making process in ASEAN countries

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ABSTRACT

Over the past few years, many innovative vaccines became available that offer protection for diseases which have never been prevented before. While there are several factors that could have an impact on access, the use of health technology assessment (HTA) undoubtedly is also one of the contributing factors. **Objectives:** To explore the landscape of vaccine access and the role of HTA in new vaccine adoption in Association of Southeast Asian Nations (ASEAN) countries. **Results:** A great deal of progress has been made in terms of access to new and innovation vaccine in the region. Variation in access to these vaccines comparing between countries, however, is still observed. The use of HTA in supporting new vaccine adoption is still in an early stage especially in Gavi, the Vaccine Alliance-eligible countries. **Conclusions:** Improving the use of HTA evidences to support decision making could accelerate the efficient adoption of new vaccine in ASEAN region.

ARTICLE HISTORY

Received 22 January 2020

Revised 7 May 2020

Accepted 9 May 2020

KEYWORDS

Vaccine; access; health technology assessment; ASEAN; national immunization program; expanded program in immunization

Introduction

Vaccines are one of the most cost-effective health interventions. With numerous efforts made to improve access to vaccine and immunization program, for example, the implementation of World Health Organization (WHO) Expanded Program in Immunization (EPI), the establishment of the Gavi and the Immunization Agenda 2030 (IA2030),¹ situation of access to vaccines and immunization services around the globe has shown a promising progress. With the advance in biotechnology, more innovative vaccines, which are new vaccines that involve the use of new antigen to protect the diseases that could not be prevented before, for example, dengue vaccine, and the combination of previously used vaccines into a new product become available.² These innovations aim at better and broader protection of human against disease as well as increasing compliance and coverage for vaccines.

Health technology assessment (HTA) is a form of policy research which systematically integrates evidence-based studies from multidisciplinary fields.³ The aim of HTA is to provide useful evidence on the optimal use of limited health resources and ensures effective, efficient, and equitable access to technologies in those countries.⁴ HTA plays a crucial role in decision making for vaccine introduction in the country. Since universal health coverage (UHC) policies need sufficient evidence for policy making, HTA

can facilitate the process to weigh different criteria such as population effects of vaccine to disease, and budget to guide decision makers on adopting new vaccines especially in the low- and middle-income country (LMICs).⁵

Association of Southeast Asian Nations (ASEAN) is the region home to ten countries including Thailand, Malaysia, Singapore, Vietnam, Laos, Cambodia, Myanmar, Brunei, Philippines, and Indonesia. The income level in the region is very diverse from high-income countries (HICs) like Singapore and Brunei to low-income countries (LICs) like Myanmar and Laos.⁶ Also geographical and population sizes differ one of the most populous regions in the world which poses challenges. The disease pattern in this region is, however, very similar especially infectious diseases.⁷ The overall objective of this article was to provide an overall description of access to vaccine, focusing on the new and innovative vaccines among countries in the ASEAN region. By extracting data of vaccine introduction and HTA processes within countries from Gavi, World Health Organization database, government official websites, and peer-review journal articles, we began our analysis with “Where are we?”, a description of current situation of access in terms of vaccines that are currently listed in national immunization program (NIP).⁸ We then explored HTA decision framework for the introduction of new vaccine into the country. Challenges in access to new and innovative vaccines were then analyzed

to investigate the role of HTA in decision-making process in these countries.

Where are we?

Current situation of access to new and innovative vaccines in ASEAN region

Emerging vaccines

In the past 15 years, several new vaccines became available in the market including rotavirus in the year 2006 (RotaTeq, Merck), human papilloma virus (HPV) in the year 2006 (Gardasil, Merck), pneumococcal vaccine (PCV) in the year 2000 (Prennar7, Pfizer), and dengue vaccine in the year 2015 (Dengxavia, Sanofi).⁹ Most of these breakthrough innovations offer protection against infectious diseases that have never been prevented before. Currently, rotavirus, HPV, and PCV vaccine are recommended by WHO Strategic Advisory Group of Experts on Immunization (SAGE) to be included in NIP in every country while dengue vaccine is recommended for only high-risk population.^{6,8} Variation in access to these vaccines, however, was found when comparing NIP in ASEAN countries. HPV vaccine is an emerging vaccine that has been included in most NIP (seven out of ten ASEAN countries) including Singapore, Thailand, Malaysia, Brunei, Philippines, Indonesia, and Lao PDR.^{10–15} NIP in six countries including Cambodia, Indonesia, Lao PDR, Myanmar, Philippines, and Singapore have already included PCV in their immunization schedule.^{15–19} Rotavirus vaccine is currently included in only one NIP, Thailand and is under planning to be included in Lao PDR, Myanmar, and Vietnam NIP.^{6,15,20} Dengue vaccine even though protect citizens from one of the most common infectious diseases in the region is currently included in Philippines NIP and are planned to be included in Indonesia NIP⁶ as listed in Table 1.

Comparing between countries, access to emerging vaccines is highest in Philippines (three out of four emerging vaccine analyzed in this article) while Vietnam even in Gavi-eligible countries still have no access to any of these emerging vaccines. The time of implementation has shown that Singapore is one of the fastest countries implementing new vaccines into their NIP.

The variation in access across countries is partly explained by the variation in prices of these vaccines in the region. Differences of vaccine prices can be as high as 30 times differences as found in PCV and rotavirus vaccine. Prices of PCV are approximately 111 USD in Singapore and

a subsidized donor price of 3 USD in Gavi-eligible countries.^{27,28} Rotavirus vaccine's prices also show the same trend as prices were reported highest at 70 USD in Singapore and lowest in Gavi-eligible countries at 2 USD.^{27,28} Anecdotal reports have shown that the vaccine price is partly determined by the country's affordability and its negotiation power and decision framework for reimbursement process.

Combined vaccines

Despite not an emerging vaccine, combining vaccines into one single product has also been an interest in immunization program around the globe. Advantages of combined vaccine include fewer injection and thus higher compliance rate especially for complex immunization schedule, better vaccination coverage and timely vaccination, lower vaccine administration cost as well as storage and cold chain requirement for vaccine.²⁹ Diphtheria, tetanus, and pertussis-based (DTP-based) vaccine is the combined vaccine that has been used in the immunization program around the globe since 1948.²⁶ With an advanced in biotechnology, inactivated polio vaccine (IPV), *Haemophilus influenzae* vaccine (Hib), and hepatitis B vaccine (HepB) are added to the DTP-based vaccine. The most recent combined vaccine was commercialized into the market in the year 2018 in the US which combine DPT vaccines with inactivated poliovirus, *H. influenzae* type b and hepatitis b.⁹ Currently, all countries in ASEAN have used at least pentavalent DTP-based vaccine in their immunization schedule except Brunei in which hexavalent DTP-based vaccine has already been included in NIP. For pentavalent DTP-based vaccine, DTwP-Hib-HB vaccine is currently used in NIP in seven out of ten countries including Thailand, Indonesia, Cambodia, Philippines, Lao PDR, Myanmar, and Vietnam while DTaP-Hib-IPV vaccine is currently used in NIP in Singapore and Malaysia.^{6,30} The extent in which pentavalent- and hexavalent-based vaccine is first implemented in NIP in ASEAN countries is more than 10 years in which Malaysia is the first country to include DTaP-Hib-IPV in 2008 and Thailand is the last country to include DTwP-Hib-HB in 2019.^{31,32} Differences in prices of combined DTP-based vaccine were found similarly to other emerging vaccines as prices in self-funded countries and Gavi-eligible countries vary considerably. Prices of DTwP-Hib-HB are 24 USD in Thailand and 1 USD as a subsidized donor price in Gavi-eligible countries.^{24,28}

HTA decision framework for the introduction of new vaccine into the country

We used new vaccine adoption decision-making frameworks developed by Burchett et al. and identified HTA-related

Table 1. Access to vaccine through national immunization program among ASEAN countries.

	Singapore	Thailand	Malaysia	Brunei	Philippines	Indonesia	Cambodia	Lao PDR	Myanmar	Vietnam
Emerging vaccines										
PCV	2009 ¹⁴	X	X	X	2013 ¹⁴	2017 ¹⁴	2015 ¹⁴	2013 ¹⁴	2016 ¹⁴	X
RV	X	2019 ¹⁹	X	X	X	X	X	(Planned) ¹⁴	(Planned) ¹⁴	(Planned) ¹⁴
HPV	2010 ^{12,14}	2017 ^{11,14}	2010 ^{13,14}	2012 ¹⁴	2016 ^{10,14}	2016 ¹⁴	X	2019 ¹⁴	(Planned) ¹⁴	X
CYD-TDV	X	X	X	X	2017 ²¹	(Planned) ⁵	X	X	X	X
Combined vaccines										
DTwP-Hib-HB	X	2019 ²²	X	X	2013 ²³	2013 ²⁴	2010 ²⁴	2009 ²⁴	2012 ²⁴	2010 ²⁴
DTaP-Hib-IPV	2013 ^{14,25}	X	2009 ¹⁴	X	X	X	X	X	X	X
DTaP-Hib-HB-IPV	X	X	X	Yes ^{*26}	X	X	X	X	X	X

*No data on when the vaccine is available in NIP.

Sources: World Health Organization, Gavi the Vaccine Alliance, National Immunization Program in each country.

criteria to analyze HTA role in decision-making process in the region.⁵ These criteria include the importance of the health problem (burden of disease), vaccine characteristics (safety, efficacy, and effectiveness), financial economic issues (economic evaluation and budget impact analysis), ethical, organizational, social, and legal aspects (feasibility, vaccine supply, acceptability, equity, ethics, cold-chain readiness, and vaccine management system) as listed in Table 2.

We have found that decision framework for the introduction of new vaccine in ASEAN countries is vastly different. This is due to the fact that ASEAN region houses countries with different health system context as well as decision framework for new vaccine introduction.³ Countries in ASEAN region could be sorted into two groups; the Gavi-eligible countries and countries which fully self-finance their immunization program.³³ Four countries in the region, namely Myanmar, Vietnam, Cambodia, and Lao PDR are currently eligible for new vaccines support from the Gavi. Vietnam and Lao PDR are now in preparatory transition phase of graduating from Gavi's support and to fully self-finance in 2020 and 2022, respectively to promote country ownership on national EPI.³⁷ While Cambodia and Myanmar when reach Gavi's eligibility criteria, will also have to graduate from Gavi support. In Gavi-eligible countries, only WHO-prequalified vaccines are used in the NIP and currently purchased through the mechanisms of the United Nations Children's Fund Supply Division (UNICEF SD).⁶ Indonesia has recently graduated from Gavi support in 2018. Singapore, Malaysia, Brunei, Philippines, and Thailand are countries in the region in which vaccines are self-financed using government budget and no support from the international organization.³³

In the countries where vaccines are self-financed using government budget, the HTA criteria for decision making to include vaccine in NIP are mostly clearly established.^{3,36,43} These countries usually have HTA guidelines, institutionalized HTA bodies, and require HTA to support for new vaccine adoption. Burden of disease and vaccine characteristics (vaccine safety and efficacy) are among the most common criteria used by these countries. Economic aspect of candidate vaccines considered, which is of the major criteria for decision making, are cost-effectiveness results. However, with explicit criteria set defined by the decision-making body in each country, the details of the evidences used to support decision making varies. For example, the requirement for the use of health economics modeling is different across countries. Thailand has stated clearly in the national health technology assessment guideline that health economics model is required for the HTA of vaccines preferably dynamic transmission model or typical static model while Singapore only requires health economics modeling without type of modeling specification and Malaysia do not have specific guidance for economic evaluation of vaccine.⁴⁴

HTA structure and utilization of HTA for decision-making process in Gavi-eligible countries are however, not well established. Vietnamese Ministry of Health (MoH) has just started conducting HTA as well as reviewing evidences from the published literature. However, HTA has not been fully and formally utilized for regulatory and reimbursement decisions for health technologies with vaccine being no exception.⁴ In

Lao PDR, there is a lack of capacity in HTA. It was found that there have been no changes to the benefit packages for the public insurance health benefit schemes in recent years.⁴⁵ In Myanmar, the use of HTA to support decision-making process was reported, as cost-effectiveness analysis played a crucial role in the policy adoption of Maternal and Child Health Voucher Scheme in which infant immunization is a part of the program.⁴⁶ However, the use of HTA in a routine decision made by the government is still far from the ideal. In Cambodia, the availability of evidences and data of health technology are increasing but still lack of adoption guideline resulting in weak research capacity in the country.³⁴

Next to HTA decision frameworks but related to it, the establishment of National Immunization Technical Advisory Groups (NITAGs) in each country is worth mentioned here. NITAGs have been established in all countries in the region except for Brunei.³⁰ However, a wide range of the time NITAGs first established in these countries were found. The NITAGs have been in existence in Thailand since 1970, while the establishment of NITAGs in Cambodia was not long ago in 2016.⁴⁷ Therefore, the structure of NITAGs as well as the policy process each NITAGs involved in is varied by level of establishment. It is not clear in the literature how much NITAGs and HTA processes are interrelated in these countries. Even the roles of NITAGs maybe different between countries but the overall objective of NITAGs is mainly to assess evidences regarding the vaccine, as well as review and recommend evidence-based immunization policies.⁴⁸ With the different experience level of NITAGs in this region, the use of evidences like HTA in supporting decision making to adopt new vaccine would be different.

Vaccine and disease characteristics

In order to observe the role of HTA in decision-making process of emerging vaccines in the region, we summarize the evidences available from some these vaccines as well as the disease the vaccine is preventing as an illustration.

Pneumococcal conjugate vaccine (PCV)

Pneumococcal infection is an infection that can lead to serious complications such as meningitis, septicemia, and pneumonia. A pneumococcal conjugate vaccine containing 7 serotypes (PCV-7) came on the global market in 2000.⁹ In 2009 and 2010, two more pneumococcal conjugate vaccines were launched into the market with more serotypes added; the 10-valent (PCV-10) and the 13-valent (PCV-13) vaccines.⁹ Since then PCV-7 is gradually being removed from the market as it was replaced by the two new PCVs. Both PCV10 and PCV13 have been shown to be safe and effective and WHO recommends the inclusion of PCVs in childhood immunization programs worldwide.⁸ In terms of the burden of the disease, Indonesia, Vietnam, Philippines, and Myanmar are among the top 15 countries worldwide reported with the highest number of new cases of clinical pneumonia in 2008.⁴⁹⁻⁵¹ Several clinical studies of PCV vaccine in Singapore, Thailand, Lao PDR, Malaysia, and Cambodia have demonstrated good safety profile of the vaccine as well as its efficacy

Table 2. Decision framework for the introduction of new vaccine.

	Singapore	Brunei	Thailand	Malaysia	Philippines	Indonesia	Cambodia	Lao PDR	Myanmar	Vietnam
Gavi-eligible country (Gavi-graduating year) ³³	No	No	No	No	No	Recently graduated (2018)	Yes (TBC) 2016 ²⁶	Yes (2022) 2013 ³⁴	Yes (TBC) 2009 as NCIP ³⁴	Yes (2020) 1998 ³⁴
NITAGs establishment	1975 as EC ³⁴	No ²⁶	1970 as ACIP ³⁴	2008 as NCIP ³⁴	1986 as NIC ²³	2007 as ITAGI ³⁵	2016 ²⁶	2013 ³⁴	2009 as NCIP ³⁴	1998 ³⁴
Decision makers regarding new vaccine adoption ³	MoH	MoH	NEDL	NCIP	DoH	ITAGI	NITAGs	NITAG	MOHS	MoH (HITAP)
HTA guideline	No	No	Third edition expected in 2020 ³⁶	Health Technology Assessment Manual 2015 ³⁷	Draft guideline ³⁸	Health Technology Assessment Guideline 2017 ³⁹	No	No	No	No
HTA agency	ACE ⁴⁰	No	HITAP ³⁶	MaHTAS ³⁷	Yes (not named yet) ³⁸	InaHTAC ³⁹	No	No	No	No
Required HTA for new vaccine adoption in NIP	Yes ⁴⁰	No	Yes ³⁶	Yes ³⁷	Yes ³⁸	Yes ³⁹	No	No	No	No
The importance of the health problem	BOD ⁵	N/A	BOD, Severity of diseases ^{5,41}	BOD	N/A	BOD ⁴²	N/A	N/A	N/A	N/A
Vaccine characteristics	Safety and efficacy ⁵	N/A	Safety and efficacy ^{5,41}	Safety and efficacy ³⁷	Safety and efficacy ²	Effectiveness and safety ⁴²	N/A	N/A	N/A	N/A
Financial economic issues	EE ⁵	N/A	EE ^{5,41}	EE ³⁷	EE ²	EE, Sustainability, Financing ⁴²	N/A	N/A	N/A	N/A
Ethical, organizational, social, and legal aspects	N/A	N/A	- Equity - Target age group ⁴¹	- Strategy for service - Delivery - Monitoring and surveillance - Regulatory ³⁷	N/A	- Vaccine availability - Capability to produce the vaccine (in some vaccine) ⁴²	N/A	N/A	N/A	N/A

*SIVAC has been supporting the strengthening of the committee since September 2010.

TBC = To be confirmed, EC1 = Expert Committee on Immunization, MoH = Ministry of Health, ACIP = the Advisory Committee on Immunization Practices, NEDL = Health Promotion and Disease Control and National Essential Drugs List, NCIP = the National Committee on Immunization Practices, NIC = The National Immunization Committee, DoH = Department of Health, ITAGI = the Indonesian Technical Advisory Group on Immunization, NITAGs = National Immunization Technical Advisory Groups, MOHS = the Ministry of Health and Sports, HITAP = The Health Intervention and Technology Assessment, ACE = Agency for Care Effectiveness, MaHTAS = The Malaysian Health Technology Assessment Section, InaHTAC = Indonesian Health Technology Assessment Committee, BOD = Burden of Disease study, EE = Economic Evaluation study, N/A = Not applicable

Sources: World Health Organization, Gavi the Vaccine Alliance, HTA report in each country, NITAGs resource center.

against invasive pneumococcal diseases (IPDs).^{16,52–54} However, several cost-effectiveness analyses of PCVs conducted in Singapore, Malaysia, and Thailand have shown that PCVs usually PCV-10 and PCV-13 are a cost-effective strategy.^{55–57} Cost-effectiveness analysis in Singapore has shown that PCV-7 is a very cost-effective strategy while PCV-10 and PCV-13 are moderately cost-effective strategy. In Thailand, PCV-10 and PCV-13 are cost effective when considering herd effect. The results were found similar findings in Malaysia. These three studies found common characteristics that the inclusion of herd immunity effects would change the incremental cost effectiveness ratio substantially more favorable.

Rotavirus vaccine (RV)

Acute diarrhea in infant or childhood is typically caused by rotavirus that infects the gastrointestinal tract called “Rotavirus gastroenteritis.”⁵⁸ The incidence of infection is resembled in ASEAN countries member in which diarrhea and gastroenteritis is common and approximately 15 cases per 1,000 children are hospitalized annually for acute gastroenteritis.⁵⁹ WHO recommends the inclusion of rotavirus vaccine in NIPs worldwide especially in high-risk country.⁸ However, rotavirus vaccine evidences conducted locally in Singapore, Indonesia, Thailand, Vietnam, and Malaysia showed controversial efficacy and safety data.^{60–62} Efficacy in Indonesia is lower than estimated in other countries while safety data are available in Singapore only.^{60,63} No serious adverse events occurred. Several economic evaluation studies for rotavirus vaccination were conducted in Lao PDR, Indonesia, Cambodia, Myanmar, Malaysia, Thailand, Philippines, and Vietnam and most found that the vaccine is a cost-effective strategy.^{63–65}

Human papillomavirus (HPV) vaccine

Human papillomavirus (HPV) is a group of more than 100 types of virus infection that spread throughout the world. The infection can commonly be transmitted by sexual activity and can possibly contribute to cancerous cervical lesions and turn to cervical cancer.⁶⁶ WHO reported that two types of high-risk HPV (16 and 18) cause 70% of cervical cancer worldwide.⁶⁷ The primary prevention strategy is HPV vaccine injection for girls between 9 and 4 years before first sexual intercourse.⁶⁸ Bi- and quadrivalent HPV vaccine become available on market since 2009 and 2014, respectively.⁹ Both of them have been shown to be safe and effective in several studies from Thailand, Indonesia, and Malaysia.^{69–71} From a review by Arbyn et al., excellent protection from cervical precancer is found in bi- and quadrivalent vaccine and the efficacy is lower in middle age women (24–45 years).⁷² Several economic evaluation studies for HPV immunization were conducted in Lao PDR, Indonesia, Malaysia, Singapore, Thailand, and Vietnam and most found that the vaccine is a very cost-effective strategy.^{69,73–77}

Dengue vaccine (DV)

Dengue is the most frequent and rapidly spreading mosquito-borne virus that affects countries in the ASEAN region greatly. In 2019, there were 124,751 reported dengue cases in Vietnam, 95,000 cases in Thailand and 110,399 cases in Malaysia.^{32,78} The need for a dengue vaccine is more pressing than ever. Currently, there is only one dengue vaccine available in the market. Two large phase 3 trials which were conducted in Philippines, Indonesia, Vietnam, Malaysia, and Thailand have shown that overall efficacy of vaccine is 56.5% and can lower the risk of dengue hemorrhagic fever by 80%.^{79–82} The efficacy is however changed by the immune status of the recipients; 74.3% in previously exposed patients vs 35.5% in naive patients.⁸³ This finding has implications for vaccine introduction and implementation as the SAGE recommended a “prevaccination screening strategy” to be included as a dengue vaccination program, in which only dengue-seropositive persons are vaccinated.⁸⁴ Several economic evaluation studies for dengue vaccine were conducted in Indonesia, Malaysia, Singapore, Thailand, and Vietnam and most found that the vaccine is a cost-effective strategy.^{85,86}

Combined vaccine

The use of combined vaccine depends mainly on whether to include the additional vaccine in the NIP. According to WHO recommended vaccines worldwide, diphtheria, pertussis (whooping cough), and tetanus (DTP) containing vaccine is listed in NIP in every ASEAN member countries for decades same as other vaccines such as polio (OPV/IPV) vaccine and hepatitis B (HepB) vaccine. But some are recently included to the programs in a last few years such as *H. influenzae* type b (Hib) vaccine in Thailand.^{8,9,32}

Challenges in access to new and innovative vaccines

Access to new vaccines in the region face several challenges

Before addressing these challenges, it should be noted that access to vaccine in this study is limited to access through NIP in the public sector but not through the private sector. We have found that challenges in access to new and innovative vaccines vary by health system context of each country as well as evidences available for each vaccine and the disease the vaccine is preventing. The situation of access to new vaccines in the region is not low since many countries especially low-to-middle-income countries have access to most new and innovative vaccines through Gavi. The major challenge is however, how to sustain the progress in access to these vaccines especially after graduating from Gavi support in particular in large countries like Indonesia. The case of access to PCV vaccine is a good illustration of this challenge. The use of PCV vaccine in self-financed countries is low with Singapore and Philippines being the only two countries provide PCV vaccine for free under their NIP.^{6,15} The expansion of access in region is therefore through countries whose PCV vaccine is

supported by Gavi. This echoed the situation observed around the globe in which children in some of the countries with the weakest economies are actually better protected against infectious disease than are those in some wealthier countries. As income in these countries grows and at the same time the cut in external support is anticipated, these countries could face the same challenges as wealthier countries with fewer resources.

Another challenge is the HTA evidences around vaccine and immunization programs for introduction decisions. HTA evidences conducted locally could have an impact on the decision to adopt vaccine into NIP. For example, HTA evidences of rotavirus vaccine have shown good safety profile and vaccine efficacy around the globe. Local data, however, have shown that efficacy in some country in the region may not be the same as those reported globally. As a result, the vaccine has been first adopted recently in only one country, Thailand.⁶ The other reason that may delay the adoption of rotavirus vaccine especially in Islamic countries like Indonesia is the local cultural and religious value of vaccine itself. Local HTA evidence has shown that the absence of “Halal” labeling is not deemed acceptable and rotavirus will not be included in NIP unless halal certified rotavirus vaccine becomes available.⁸⁷ Another example of how HTA evidences could impact decision making by NIP is the case of dengue vaccine. Even though dengue infection is one of the most common infections in the region and the region is in desperate need for dengue infection prevention, the implementation of vaccine in real world is complicated. The efficacy data of the vaccine show that the protection of dengue infection depends on the immune status of the recipients. Therefore, the “pre-vaccination screening strategy” is required and this administrative barrier may be one factor delaying access to dengue vaccine in the region. The other important factor might be related to the concern of the safety of dengue vaccine as it has been reported after the implementation of dengue vaccine in the Philippines.⁸⁸ It is obvious from this finding that HTA evidences may not be the only factor that affects access to new and innovative vaccine but if HTA evidences do not meet the pre-specified criteria especially the uncertainties in safety and efficacy profile of the vaccine, the vaccine is unlikely to be adopted. For HPV vaccines evidence around implementation challenges are around vaccinating adolescent girls outside traditional EPI programs. The optimal delivery strategy and cost implications poses issues for countries considering introducing HPV vaccines, in addition to procurement prices for non-Gavi-eligible countries.^{89,90}

Capacity of the local country to conduct HTA or appraise HTA evidences from other sources could become a major challenge in the future. Vaccines used in Gavi-eligible countries are selected for recommendation based on donors and technical agencies’ preferences and priorities (e.g., Gavi, WHO, and UNICEF). Since these countries will finally graduate from the support, the use of HTA evidences to support decision making is necessary to sustain programs in particular when countries graduate from donor support. HTA evidences for vaccine is complex and the availability of local data could have changed the decision in some cases. Take PCV, for example, even though HTA evidences is

strong that pneumococcal infection is common in the region and clinical study shows good efficacy against the infection, local data on serotype prevalence of pneumococcal infection and possibilities of cross-effect between different serotypes is not readily available in many countries in the region. Cost-effectiveness results of PCV also depend mainly on the inclusion of herd immunity effect in the analysis. The inclusion of herd immunity using static model can only be considered reliable if high-quality surveillance data are incorporated into the analysis. The inclusion of these kinds of analysis needs skilled researchers to conduct, appraise, and translate the results into policy. The latter example raises another issue of HTA structure available in the region. Even though, we have found that most countries in this region have established NITAGs to support decision making regarding immunization service, it is clear that most Gavi-eligible countries are far behind from having the HTA structure required to support local decision making. This includes not only an HTA unit and skilled researchers but also local data needed for the HTA.

Unquestionably, one of the contributing factors to access is the price of the vaccine. We have found that variability of vaccine’s price in the region is high especially when comparing the price of vaccine procured by local government and the price of vaccine procured by Gavi for Gavi-eligible countries, for example, price of rotavirus vaccine in Singapore can be as high as \$USD 100 per dose²⁷ compare to \$USD3 per dose procured by Gavi.²⁸ Also, when price of the vaccine is considered high, even when most local cost-effectiveness results have shown that the vaccine is a cost-effective strategy, the vaccine would not be included in NIP. Situation of access to rotavirus vaccine is a good instance. Access to rotavirus vaccine as aforementioned is low. This phenomenon however is observed in other parts of the world as the majority of countries (57%, 110/194) had not introduced universal rotavirus vaccine and high-income countries, on average, had poorer rotavirus vaccine coverage compared to low and lower-middle income countries.²¹ Contributing factors of low access to rotavirus vaccine may be due to several reasons including low perceived risk of disease, safety concerns around intussusception, and lastly the pricing of the vaccine and the budget impact and financial sustainability. The situation of access may change since new rotavirus vaccine from other manufacturers in India and Indonesia become available in the market and as a result, a lower vaccine price and acceptable to Islamic countries.

For vaccines that already have high access like HPV vaccine, the challenge for HPV vaccine is not on whether to include HPV in NIP but on how to sustainably implement the vaccine in the country’s immunization schedule. In Thailand, HPV vaccine is currently available for free under NIP for girls age 11 years old while eligible population for HPV vaccine in Malaysia is 13 years old.³⁰ With this variation in immunization schedule, countries will need to consider the expansion of eligible population as well as delivery strategy, for example, school-based program versus catch up program, number of doses provided, the supply security of the vaccine available from the manufacturer, and lastly the long-term financial sustainability.

Lastly, time to first introduction could be accelerated for faster access. Combined vaccine, for example, even has already been included in NIP in every country in the region. The time of first introduction, however, is lengthy as the first country to introduce combined vaccine was Malaysia in 2008 and the last country, Thailand, was in 2019.^{31,32} This may be due the fact that the price of these vaccine is considerable high among others such as 33 USD for DTaP-Hib-IPV in Thailand.²⁴ Availability of local data on HTA evidence again could accelerate faster adoption of new vaccine. It is obvious that HTA structure, for example, HTA body, the use of evidenced-based information to support new vaccine adoption in these countries is still not established. Capacity building for evidences generation and evidences appraisal will then cannot be overlooked.

Future directions

A great deal of progress was made in increasing access to new and innovative vaccine in this region. Still, some of these emerging vaccines have not been introduced in most countries in the region. To expand access to new and innovative vaccine for this region should center on improving the use of HTA evidences for new vaccine adoption. Decision framework or system to support decision in all ASEAN countries should be set up and link with global initiatives such as the Decide Health Decision Hub established in 2019 to facilitate online meeting space for people working on supporting decision making in health through an evidence-based process.²² Since some countries in ASEAN already have an established HTA system and expertise, for example, Thailand,⁴³ developing countries can use lesson-learned or developed tools and implement them in their country. Data and information can also be shared as some of the characteristics of the population in the region is not much different. HTA data sometimes can therefore be generalizable from country to the other. Data sharing can also include the sharing of pricing data or further develop to the implementation of pool procurement in the region. Some of these initiatives have already been ongoing as Gavi financially supports eligible and transitioning countries with health systems strengthening grants (HSS). The objective of Gavi HSS support is to address system bottlenecks to achieve better immunization outcomes, including increased vaccination coverage and more equitable access to immunization. Another movement that has been initiated in the strengthening and sustaining of NITAGs globally. This includes intercountry NITAGs collaboration, the founding of Global NITAGs Network (GNN),²³ and the launch of the updated NITAGs Resource Center (NRC)²⁵ and in the future the potential of having Regional Technical Advisory Groups on Immunization (RTAGs) and regional networks.²⁵ If the HTA structure is to be further established, future efforts should be focused on expediting the research and development of vaccines for disease that meet the needs of the region and country requirement, for example, halal certified vaccine, local infectious disease using different tools, for example, WHO's CAPACITI (Country-led Assessment for Prioritization of Immunization) project which will use HTA frameworks and evidences on supporting countries in the

process of decision making (deliberate processes using multi-criteria decision analysis: MCDA) for prioritization of vaccines.³⁵

This review emphasizes how international donor like Gavi played a major role in increasing access in this region and how HTA evidences played a role in access to emerging vaccine in self-financed countries. Yet there is still a need to further increase access to new vaccine as well as expand coverage to these vaccines, in both Gavi and non-Gavi countries.

Acknowledgments

RH is a staff member of the WHO. The views are his and do not necessarily represent the views of the WHO.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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