The ASEAN Vaccine Baseline Survey (AVBS)
Current Situation and Gap Analysis

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The ASEAN Vaccine Baseline Survey (AVBS)

Current Situation and Gap Analysis

The ASEAN Secretariat
Jakarta

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ASEAN: A Community of Opportunities for All

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Introduction:

The ASEAN Vaccine Baseline Survey (AVBS) was one of the recent interventions conducted by the National Vaccine Institute (Public Organization), Thailand (NVI) to partially fulfill Thailand's commitment to ASEAN as the assigned lead country and focal point for ASEAN Vaccine Security and Self-Reliance (AVSSR). The Survey aimed to describe the most current capacity, gap and/or challenges in relation to the whole vaccine value chain, i.e. research and development (R&D), production, regulation and immunisation, at regional and country levels within ASEAN.

The AVBS is the first in the series of five (5) activities stipulated in the ASEAN Health Cluster III (AHC3) Work Plan for 2016-2020 on Strengthening Health Systems and Access to Care and under the Health Priority 17 on Pharmaceutical Development. It was endorsed for implementation by the 2nd ASEAN Health Cluster 3 Meeting in Manila, Philippines during 5-6 July 2017. Based on in the Work Programme the AVBS was planned to begin and finish within 2017, followed by the second activity to develop regional strategies and action plans to achieve AVSSR. The AVBS was placed at the very first step of the AVSSR implementation, for the results of the survey to be used to support the formulation of strategies and action work plans in achieving AVSSR.

This report was compiled after the aforementioned AVSSR workshop on 28-30 March 2018 or the "AVSSR Workshop 2018" at the Grand Mercure Bangkok Fortune Hotel in Bangkok, Thailand was held. The workshop was attended by vaccine experts and officials from all ASEAN member states (AMS). The NVI team shared with them the preliminary findings of the AVBS 2017, ascertained the accuracy of the verified data and collected new information from the participants. The contents of this report were based on the information collected from all sources until the end of March 2018. This was to ensure that the most recent ASEAN vaccine baseline information is well captured.

Methodology:

The data used and presented in this report were from multiple sources. These were collected through four (4) main channels from 1) the AVBS 2017, 2) country expert interviews, 3) field visits to potential vaccine manufacturers in selected AMS and 4) desk research from relevant previous surveys and internet-searchable sources. It must be noted that the relevant data from sources other than the AVBS 2017 were selectively used to supplement the missing or unclear information from the AVBS 2017 survey template.

The AVBS 2017[1] collected primary data directly from AMS through a self-administered Microsoft Excel® template which consisted of seven (7) work sheets with nine (9) tables in accordance with the four (4) designated areas of vaccine value chain i.e. vaccine research and development, production, regulation and immunisation. The AVBS template is available at: http://www.nvi.go.th/index.php/blog/2017/01/AVBS_2017. The template was distributed by the ASEAN Secretariat (ASEC) to the Focal Points of ASEAN Health Cluster 3 on 17 July 2017 and requested that the duly submit completed templates to NVI by 30 September 2017.

In 2017, NVI conducted four (4) expert interviews, one expert each from Indonesia and Myanmar, and two from the Philippines on 28 April[2], 15 June and 4 July [3], respectively. Three field visits to potential vaccine manufacturers in several AMS were conducted in the Philippines (4 July)[3], Vietnam (6-10 November)[4], and Myanmar (20-22 December)[5]. Relevant information and data from previous surveys, e.g. results of the self-administered questionnaire survey conducted in Phuket, Thailand during the October 2014 Workshop on ASEAN Regional Vaccine Security [6], and from the internet search engines were also reviewed and used as needed.

In addition, the AVSSR Workshop 2018, which was held on 28-30 March in Bangkok, Thailand, provided an opportunity to incorporate additional data for the AVBS 2017. Relevant data on current capacity and challenges on vaccine development, production, regulation, and immunisation obtained from AMS presentations were noted and incorporated as appropriate to the preliminary findings of the AVBS 2017.

Results:

It should be noted that due to the amount and extent of information required, informants in AMS took more time than expected to provide the answers as per AVBS 2017 template (approximately 6 months late with several times of deadline extension). As a result, analysis of the results had to be delayed until late February 2018 since the NVI team had to report preliminary findings of AVBS 2017 to participants of the AVSSR Workshop in March 2018.

By the end of February 2018, all AMS except the Philippines have sent their answers to NVI making the analysis possible. Only three (3) countries (Malaysia, Singapore and Thailand) provided data in all the four areas of vaccine value chain as required, while the rest provided data in some areas. On the involvement of key informants in the four (4) main areas of vaccine R&D, production, regulation and immunisation, it was found that the proportion of area-specific key informants is higher than non-area specific key informants (14/11) based upon respondent countries and completed areas (see Table 1).

In fact, the high frequency of area-specific respondents reflected the reliability and accuracy of the data for further analysis. However, identification of key informants in inactive areas where data might not be available proved to be a challenge for some AMS. In the future, this barrier needs to be overcome for better results. For a "missing" country like the Philippines, information was mostly derived from the country presentation in the AVSSR Workshop 2018.

Table 1 Characterization of the AVBS respondent countries

ASEAN countries	Respondent country	Completion of the AVBS survey template	Vaccine Value chain and key informant's involvement in specific areas			
			R&D	Production	Regulation	Immunization
Brunei Darussalam	+	-	√‡	√ ‡	√†	N/A
Cambodia	+	-	N/A	N/A	N/A	√†
Indonesia	+	-	N/A	N/A	N/A	√†
Lao PDR	+	-	√‡	N/A	√†	N/A
Malaysia	+	+	√†	√‡	√†	√†
Myanmar	+	-	N/A	√†	√‡	√†
Philippines	N/A	N/A	N/A	N/A	N/A	N/A
Singapore	+	+	√‡	√‡	√‡	√†
Thailand	+	+	√‡	√‡	√‡	√†
Viet Nam	+	-	√†	√†	√†	N/A

Symbols:
The involvement of key informants characterized by
†: inside specific area
‡: outside specific area

1. General profile of ASEAN and its member states (AMS)

In this baseline assessment report, the general assumption was based on the current capacity on vaccine production and was applied to categorize all AMS into 2 main groups which consisted of 1)**vaccine producing countries** i.e. Indonesia, Myanmar, Singapore, Thailand and Viet Nam, and 2)**non-vaccine producing countries** i.e. Brunei Darussalam, Cambodia, Lao PDR, Malaysia and The Philippines. To better understand the results of report, the four (4) areas of 1) vaccine (R&D), 2) production, 3) regulation and 4) immunisation were elaborated and aligned with the proposed two (2) groups.

With regard to vaccine production capacity in Singapore, the GlaxoSmithKline (GSK), a private vaccine company, manufactures only active ingredients (bulk vaccine) for Pneumococcal conjugate vaccine (PCV). However, this bulk vaccine is transported to the GSK's plant in Belgium to complete the production processes. For this reason, Singapore has been classified as one vaccine producing countries in ASEAN.

Basically, AMS are economically - diverse where each AMS performance and investment capacity is different. According to the International Monetary Fund's (IMF) 2017 ranking [7], Brunei Darussalam and Singapore are the two high-income countries while all the rest are middle-income countries (MICs). Among ASEAN MICs, Malaysia and Thailand are upper middle-income countries (UMICs) while Cambodia, Indonesia, Lao PDR, Myanmar, the Philippines and Vietnam are lower middle-income countries (LMICs). ASEAN has high chance of success in aiming to achieve AVSSR in the region since all AMS are attaining quite good or satisfactory economic status.

The population profile table describes vaccine producing and non-vaccine producing AMS and list of Communicable Diseases under the National Surveillance and Disease Control System among the AMS are presented in Table 2 and Table 3, respectively.

Table 2 AMS population profile (estimates for 2018)

ASEAN Population (652.19 millions)			
Vaccine Producing countries		Non-vaccine producing countries	
Indonesia	265.30	Brunei Darussalam	0.43
Myanmar	53.02	Cambodia	16.25
Singapore	5.74	Lao PDR	6.78
Thailand	69.18	Malaysia	32.50
Viet Nam	94.58	Philippines	108.39

Source: http://www.statista.com/statistics/796222/total-population-of-the-asean-countries/

Regionally, an estimated population of 652.19 million was documented in 2018. The top five (5) ASEAN countries with the highest population (in millions) are Indonesia (256.30), the Philippines (108.39), Viet Nam (94.58), Thailand (69.18) and Myanmar (53.02). In contrast, the lowest population among AMS was recorded in Brunei Darussalam (0.43), followed by Singapore (5.74) and Lao PDR (6.78). Focusing on the total ASEAN population, it was deemed more reasonable to consider the regional numbers in production of vaccines in order to meet economies of scale rather than production for one country.

Table 3 List of communicable diseases under the National Surveillance and Control System among AMS

List of Communicable Diseases	Vaccine producing countries				Non-vaccine producing countries					Fequency
	Indonesia	Myanmar	Thailand	Viet Nam	Brunei Darussalam	Cambodia	Lao PDR	Malaysia	Philippines	
Acute respiratory infection		√							√	2
Adenoviruses				√						1
Anthrax							√			1
Chickenpox				√	√					2
Dengue		√	√	√	√	√	√	√	√	8
Diarrhea	√	√	√	√		√	√		√	7
Diphtheria							√			1
Dysentery/Shigellosis/Amoebiasis		√		√		√				3
Gastroenteritis					√					1
Gonorrhea								√		1
Hand Foot Mouth Disease (HFMD)			√	√	√			√		4
Hemorrhagic conjuntivitis			√							1
Hepatitis B		√	√		√			√		4
Hepatitis C								√		1
Human Immunodeficiency Virus (HIV)	√	√			√	√		√		5
Influenza			√	√					√	3
Leprosy	√					√				2
Leptospirosis			√							1
Malaria		√	√	√		√		√		5
Measles		√					√	√		3
Meningitis							√			1
Mumps				√						1
Pertussis							√			1
Pneumonia	√		√			√			√	4
Polio							√			1
Scrub typhus			√							1
Syphilis					√					1
Tetanus							√			1
Tuberculosis (TB)	√	√	√		√	√		√	√	7
Typhoid							√			1
Upper respiratory infection						√				1

Source: summarized from country presentations by participating country delegates, AVSSR workshop, Mar 2018, Thailand (remarks: not attended by Singapore)

Based on the National Surveillance and Control System among AMS, data indicated that the most common infectious diseases epidemic in the Region are Dengue Virus infection, Tuberculosis (TB), Diarrhea, Human Immunodeficiency Virus (HIV), Malaria, Hand Foot Mouth Disease (HFMD), Hepatitis B and Pneumonia. However, the outbreak of vaccine preventable diseases (VPDs) e.g. Diphtheria, Measles, Pertussis or even Polio was observed to be sporadically occurring and is still noted in Lao PDR. In the future, vaccine candidates representing these kinds of infectious diseases need to be prioritized for further research and development, including production by interested parties in ASEAN in order to meet the Region's needs.

2. Vaccine-related R&D capacity profile

2.1 Vaccine research institutes and on-going medical pathogens for vaccine R&D

Quite a few vaccine-related research and development (R&D) activities were conducted in more than half of AMS, both the currently vaccine producing and non-vaccine-producing countries, as listed in Table 4 and Table 5.

Table 4 Current capacity on vaccine research and development in vaccine producing AMS

ASEAN countries	Capacity on vaccine R&D	Research Institues/organizations	Medical pathogens for vaccine R&D
Indonesia	+	PT BioFarma	*Streptococcus pneumoniae* or Pneumococcal
Myanmar	+	Department of Medical Research, Ministry of Health and Sports	N/A
Singapore	-	-	-
Thailand	+	Government Pharmaceutical Organization (GPO)	Influenza virus
			Diphtheria
			Tetanus
			Pertussis
		Center for Vaccine Development (CVD); Mahidol University	Dengue virus
		Chiangmai University	
		Vaccine Research Center (VRC); Chulalongkorn University	
		National Science and Technology Development Agency (NSTDA), Ministry of Science and Technology (MOST)	
		BioNet ASIA	
		CVD and (GPO)	Japanese encephalitis (Live attenuated)
			Zika virus (ZKV)
		Department of Medical Science (DOMS), Ministry of Public Health	Hand Foot Mouth Disease (HFMD) - Enterovirus 71
			Hepatitis B virus
		irindhorn International Institute of Technology (SIIT), Thammasart University and NSTDA	*Mycobacterium tuberculosis* (new TB)
		National Biopharmaceutical Facility (NBF) and DOMS	*Japanese encephalitis* (Subunit)
Viet Nam	+	VABIOTECH	*Japanese encephalitis* (Vero cell)
			Haemophilus influenzae type B
		POLYVAC	Inactivated Polio virus (IPV)
		IVAC	Seasonal influenza virus (split)
			Pandemic influenza virus (H5N1, H7N9)

Symbols:
+ : Presence of vaccine R&D capacity
- : Absence of vaccine R&D capacity
N/A: Data not available

In this report, the scarcity of such evidences on vaccine research and development in Indonesia was noted, in spite of the presence of the biggest biopharmaceutical company like the PT BioFarma. There has been only one vaccine candidate known and being developed by the PT BioFarma in partnership with the Program for Appropriate Technology in Health (PATH) and Boston Children's Hospital. This is an inactivated whole cell *Streptococcus pneumoniae* (*S. pneumoniae*) or Pneumococcal. However, this missing area should be explored and addressed in the future to be part of fundamental information that will increase understanding on current vaccine R&D in ASEAN region.

Table 4 shows that the presence of vaccine research institutes is marked typically in public, academic and private sectors, while local vaccine manufacturers are simultaneously vaccine developers. Among vaccine producing AMS, Thailand and Viet Nam showed a firm capacity on vaccine research and development on several kinds of on-going medical pathogens. Whereas Myanmar's capacity on R&D, through the Department of Medical Research, Ministry of Health and Sports (MOHS), is quite limited.

In Thailand, up to ten (10) antigens classified by research institute and/or vaccine manufacturers are being researched to be vaccine candidates i.e. 1) Influenza virus, 2) *Corynebacterium diphtheriae*, 3) *Clostridium tetanus* and 4) *Bordetella pertussis* conducted by the Government Pharmaceutical Organization (GPO). A combined vaccine on Diphtheria, Tetanus and Pertussis (DTP) was successfully developed and produced by the GPO before terminating it in 2005. This was due to stringent requirement of Good Manufacturing Practice (GMP) compliance for product quality control, together with low yield of production

provided. However, the GPO is currently exerting effort to revitalize the said capacity under the National Vaccine Policy and Strategic Plan.

For the 5th, the GPO also conducts a seasonal Influenza (Flu) vaccine project with technical and financial supported by the World Health Organization (WHO). This vaccine is currently in clinical trial phase III and may scale up from seasonal to pandemic Influenza vaccine in the future. The production of Influenza vaccine is planed to be started by 2020 at a new industrial Flu plant located in Thab Kwang, Saraburi Province, with the aim of using the plant for manufacturing both vaccines of Influenza and Avian influenza.

Sixth is the most aggressive and life-threatening Dengue Virus (DV). It touches a wide array of research institute's interest as the diseases [Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS)] caused by DV infection. Such is endemic in tropical country like Thailand. Currently, no less than four (4) research institutes and one (1) vaccine manufacturer which include a) Center for Vaccine Development (CVD); Mahidol University, b) Chiangmai University (CMU), c) Vaccine Research Center (VRC); Chulalongkorn University, d) National Science and Technology Development Agency (NSTDA) and e) BioNet Asia have been working steadily on dengue vaccine research and development.

In fact, several kinds of production technology used for dengue vaccine R&D vary from unit to unit. The most favorite technologies applied by the CVD, CMU, VRC and NSTDA are whole cell live-attenuated, live recombinant (chimeric), Virus Like Particle (VLP) and Deoxy-ribonucleic acid (DNA), respectively. It is anticipated that the first dengue vaccine candidate will be able to enter a clinical trial phase I by 2022. In addition, the GPO in close collaboration with the CVD, Mahidol University is working together on the development of 7) *Japanese encephalitis* (JE) and 8) Zika virus (ZKV) vaccines.

A live chimeric JE based on the SA 14-14-2 strain using cell-based culture technology is expecting to be an innovative vaccine in order to replace an inactivated, Sucking Mouse Brain (SMB) JE previously manufactured by the GPO. At the same time, an optional technology of subunit is also applied for JE vaccine development which is conducted by the Department of Medical Science (DOMS), Ministry of Public Health (MOPH) together with the National Biopharmaceutical Facility (NBF), King Mongkut's University of Technology Thonburi (KMUTT).In terms of ZKV, it is establishing a proof of concept to characterize potential antigens (seeds) in *in vitro* and animal models for further development of vaccine candidates.

Other medical pathogens under research and development include 8) Enterovirus (EV) 71 causing of Hand Food and Mouth Disease (HFMD), 9) Hepatitis B virus (HBV) and 10) *Mycobacterium tuberculosis* (TB). So far, EV 71 and HBV is being developed by the DOMS-MOPH, and the first EV 71 vaccine candidate was initially tested in rabbit for immunogenicity and safety. A new TB vaccine for protecting adults from *Mycobacterium tuberculosis* infection is currently characterized as a basic research in Thailand conducted by the Sirindhorn International Institute of Technology (SIIT), Thammasart University, in close cooperation with the NSTDA.

In Viet Nam, local government vaccine manufacturers i.e. 1) The Company for Vaccine and Biological Production No.1 (VABIOTECH), 2) The Center for Research and Production of Vaccines and Biology (POLYVAC), 3) The Institute of Vaccines and Medical Biologicals (IVAC) play their significant roles as vaccine developers. With regard to the three (3) vaccine manufacturers, it is revealed that as much as six (6) vaccine candidates are being developed by the VABIOTECH, IVAC and POLYVAC which include JE, *Haemophilus influenzae* type B (Hib), seasonal Flu (split), pandemic Flu (H5N1 and H7N9) and Inactivated Polio Vaccine (IPV).

In brief, the VABIOTECH's pipeline for vaccine R&D composed of JE and Hib. A JE vaccine are being developed in close partnership with the InViragen, Inc. using cell-based culture with aiming to replace an obsolete technology for inactivated mouse brain derived-JE production. This vaccine candidate is currently undergoing testing in clinical trial phase III, as well as the Hib project which is undergoing clinical trial phase I. The VABIOTEC also has a plan to establish five-in-one vaccine (DTP-HB-Hib) as the existing pentavalent will soon be graduating from the Gavi the Vaccine Alliance's support by 2019. Moreover, three (3) different influenza vaccines developed by the IVAC are 1) inactivated seasonal Flu using split virion technology, 2) pandemic avian Flu H5N1 and 3) pandemic avian Flu H7N9. The clinical trial phase III of the former two have recently finished and the latter is undergoing a pre-clinical study in animal models. The last vaccine candidate developed by the POLYVAC is IPV. The conduction of phase II clinical trial for this vaccine is underway based on the most recent information presented by AMS during the workshop held in 28-30 March 2018, Bangkok, Thailand.

Based on information given by MOH, Singapore has not conducted vaccine R&D at the national level though there may be individual researchers in academic or research institutions conducting vaccine R&D. As an example, the InViragen, Inc. (acquired by Takeda America Holdings, Inc.) has a vaccine development centre in Singapore. However, information on its activities is quite limited.

Table 5 Current capacity on vaccine research and development in non-vaccine producing AMS

ASEAN countries	Capacity on vaccine R&D	Research Institues/organizations	Medical pathogen candidates for vaccine R&D
Brunei Darusalam	-	-	-
Cambodia	-	-	-
Lao PDR	-	-	-
Malaysia	+	Institute of Medical Research Kuala Lumpur	*Leptospira* spp.
Philippines	+	Research Institute for Tropical Medicine (RITM), Department of Health	*Mycobacterium tuberculosis*

Symbols:
+: Presence of vaccine R&D capacity
- : Absence of vaccine R&D capacity

Regarding Table 5, there are two (2) out of five (5) non-vaccine producing AMS i.e. Malaysia and the Philippines presented their existing capacity on vaccine R&D. The absence of current capacity on vaccine R&D was noted in Brunei Darussalam, Cambodia and Lao PDR. In Malaysia, the Institute of Medical Research (IMR), Kuala Lumpur is well recognized as a prominent vaccine research institute where the current research interest is focusing on vaccine used in protection against Leptospirosis caused by *Leptospira spp.* infection.

Meanwhile, the Research Institute for Tropical Medicine (RITM) under the Ministry of Health (MOH) is a primary, public vaccine research facility in the Philippines. In the past decade, the RITM had a long history of successful production of Bacilli Calmette-Guerin (BCG)

vaccine, strain French 1173P2 which was used for protection against *Mycobacterium tuberculosis* infection. Despite this production capacity, its possible disappearance may be due to high standard requirement of GMP compliance. However, the government is taking initiatives to resuscitate the national ownership for BCG production with financial and new machinery investment. The RITM is currently facing big challenges on old technologies, freeze-drying techniques, product quality assurance and control (QA&QC), including qualified staffs for BCG vaccine development, and is looking forward to receiving technical assistance from sophisticated partners both within and outside ASEAN region.

2.2 Essential infrastructures for vaccine R&D

In terms of essential infrastructures for vaccine R&D, for instances, animal breeding and testing and/or clinical study facilities, including pilot plant, it was found that these facilities exist in many AMS. Even in non-vaccine producing countries like Malaysia and the Philippines, such essential infrastructures for vaccine R&D are readily available, as listed in Table 6 and Table 7.

Table 6 Current capacity and availability of an essential infrastructure for vaccine research and development in **vaccine producing AMS**

ASEAN countries	Essential infrastructures for vaccine research and development			
	Animal breeding facility	Animal testing facility	Pilot plant	Clinical study facility
Indonesia*	+	+	N/A	N/A
Myanmar	N/A	N/A	N/A	N/A
Singapore	-	-	-	-
Thailand**	+	+	+	+
Viet Nam***	+	+	-	+

Symbols:
+ : Presence of essential infrastructures for vaccine R&D
- : Absence of essential infrastructures for vaccine R&D
N/A: Data not available
* Primate Research Center (PSSP) at the Bogor Agricultural University
** National Laboratory Animal Center (NLAC), Mahidol University, National Primate Research Center of Thailand (NPRCT), Chulalongkorn University, Center for Animal Research (CAR), Naresuan University, Thai SPF (specific pathogen free-eggs), Charoen Pokphand Group (CP)-Vaccine Quality Eggs (VQE), National

Current capacity on essential infrastructures for vaccine R&D was evaluated among five vaccine producing AMS. Ideally, four (4) kinds of essential infrastructure such as animal breeding and testing facilities, pilot plant and clinical study facility should be available at all vaccine producing countries for serving main research activities for both pre-clinical and clinical studies. However, with the limitation of information access, it was found that at least three out of five vaccine producing AMS have essential infrastructure for vaccine R&D i.e. Indonesia, Thailand and Viet Nam, except Myanmar as an updated information is not available and Singapore as documented previously.

With regard to the PT BioFarma, Indonesia as a biggest vaccine manufacturer in ASEAN, only two of combined animal breeding and testing facilities namely the Primate Research Center (PSSP) based in Bogor Agricultural University have been referred. Indonesia should exercise a completed essential infrastructure as listed in Table 6 in depth information on this kind of capacity should be further explored in the future to serve as baseline information on this area.

In Thailand, a completed cycle of pre-clinical and clinical studies were exercised through the existing essential infrastructures for vaccine R&D. As such animal breeding and testing facilities with a wide range of standard certifications are usually situated in academia where research activities are conducted. However, three (3) most important combined animal facilities that are currently receiving government support in order to meet the highest international standard of Organization for Economic Co-operation and Development principles on Good Laboratory Practice (OECD-GLP) for vaccine toxicological (safety) study are 1) National Laboratory Animal Center (NLAC), Mahidol University, 2) Center for Animal Research (CAR), Naresuan University and 3) National Primate Research Center of Thailand (NPRCT), Chulalongkorn University. The first two (2) institutes have produced Specific Pathogen Free (SPF) *rodents and rabbits whereas at least three types of Non*-Human Primate (NHP) like Cynomolgus macaque, Rhesus macaque and Common marmoset were produced by the NPRCT.

Several international standards certified for animal model production and services have already attained by the NLAC. These are International Standards Organization (ISO) 9001:2015, Occupational Health and Safety Assessment Series (OHSAS) 18001:2007, Association for Assessment and Accreditation for Laboratory Animal Care International (AAALAC) and OECD GLP/GLP on safety testing for drug development and health products. In addition, the same standard of AAALAC international has also been accomplished by the CAR, Naresuan University as well.

A-3 well-known pilot plants for small to large scale production of vaccines and other biological products in Thailand are 1) National Biophamaceutical Facility (NBF), 2) GPO and 3) BioNet ASIA. The first is located in the King Mongkut's University of Technology Thonburi (KMUTT), Bangkhuntein campus. The NBF also serves as a Contract Manufacturing Organization (CMO) for offering production services under the current GMP principles certified by the Thai Food and Drug Administration (FDA), with volume capacities ranging from small amount for pre-clinical R&D to larger volume for clinical trial purposes and commercialization. The NBF is a national training center which is considered to be part of Human Resource Development (HDR) for vaccine and biological production.

The second pilot plant is a collaborative project between the GPO and Faculty of Pharmacy, Silpakorn University with a primary purpose to develop and produce some particular vaccines like live-attenuated pandemic influenza (H1N1) and avian influenza (H5N2) to respond to emergency situations with technical support from the WHO. The last one is BioNet ASIA, a private vaccine company based in Ayutthaya province. Apart from being a main vaccine factory for commercially producing two kinds of acellular Pertussis (aP) and Tetanus diphtheria acellular Pertussis (TdaP), it also serves as a pilot plant for small scale production of clinical batches for human study.

The majority of clinical study facilities in Thailand are generally linked to leading medical schools, and the most recognized one is Vaccine Trial Center (VTC). The VTC is a center of

excellence belonging to Faculty of Tropical Medicine of the Mahidol University. Its reputation is widely acknowledged through the testing of the world's first commercial dengue vaccine, including the conduct of large scale clinical trials on vaccine against Human Immunodeficiency Virus (HIV) infection. Other essential infrastructures in support of vaccine R&D are Thai SPF-eggs and Charoen Pokphand Group (CP)-Vaccine Quality Eggs (VQE) for influenza vaccine development and production.

For Viet Nam, each vaccine manufacturer has its own facility for animal breeding and testing. In VABIOTECH, the animal house was established where several kinds of small and large animal models i.e. mice, guinea pigs, rabbits and monkeys are produced. Other animal breeding farms have been noted in POLYVAC and IVAC. The POLYVAC breeds monkeys and SPF rabbits, meanwhile guinea pigs, rabbits, chickens and horses are bred by the IVAC. Unfortunately, current information on international standards for animal model production and services received by three (3) Vietnamese vaccine manufacturers are not available. In terms of clinical study facilities, they are commonly located in some hospitals in Vietnam and the most well-known vaccine trial facility is the Clinical Research Center of the Pasteur Institute in Ho Chi Minh City (CRC-PIHCM).

While Singapore does not have any essential infrastructures for vaccine R&D managed or supported at the national level, the School of Chemical and Life Sciences at Nanyang Polytechnic (NYP) offers diploma courses in discplines related to vaccine R&D and production: biologics & process technology, chemical & pharmaceutical technology and pharmaceutical sciences. Graduates from these courses could potentially contribute to vaccine R&D and production[8].

Table 7 Current capacity and availability of an essential infrastructure for vaccine research and development in **non-vaccine producing AMS**

ASEAN countries	Essential infrastructures for vaccine research and development			
	Animal breeding facility	Animal testing facility	Pilot plant	Clinical study facility
Brunei Darussalam	-	-	-	-
Cambodia	-	-	-	-
Lao PDR	-	-	-	-
Malaysia*	+	+	-	N/A
Philippines**	+	+	N/A	+

Symbols:
+ : Presence of essential infrastructures for vaccine R&D
- : Absence of essential infrastructures for vaccine R&D
N/A: Data not available
* Institute of Medical Research Kuala Lumpur
** - Research Institute of Tropical Medicine (RITM), Department of Health
- Institute of Child Health and Human Development of the National Institutes of Health (NIH), University of the Philippines Manila

Among non-vaccine producing AMS, there are only two (Malaysia and the Philippines) unviellled their capacity in vaccine R&D regarding essential infrastructures. As mentioned previously, over the current roles of the IMR Kuala Lumpur in vaccine R&D, it also produces two kinds of rodents (mouses and mice) for use in pre-clinical study. Moreover, an additional animal testing facility using rabbits, guinea pigs and mice are being conducted at the RITM under the Ministry of Health of Philippines, as well as a large animal farm nurturing horses, sheep and serpentarium for production of snake antivenom.

In the Philippines, the most famous clinical study facilities noted are the Institute of Children Health and Human Development (ICHHD) under the National Institutes of Health (NIH), Universiy of the Philippines Manila and the RITM. It is found that various clinical trials of vaccines, for instance, Rotavirus vaccine, quadrivalent Flu vaccine (QIV) and Dengue vaccine have been done by both.

It is remarkable that potential for vaccine research and development in ASEAN, which is part of the AVSSR, is in place and should be nurtured well by authorities concerned, especially when collective self-reliance for the region is taken into account.

3. Vaccine Production capacity profile

3.1 Local vaccine manufacturers

Among the ten (10) AMS, there are five (5) vaccine producing countries with a total of 13 manufacturers differently located in Indonesia, Myanmar, Singapore, Thailand and Vietnam. The other five AMS (Brunei Darussalam, Cambodia, Lao PDR, Malaysia and the Philippines) have no vaccine manufacturers in their countries. Among 13 vaccine manufacturers is PT BioFarma located in Indonesia. It is a biggest and foremost state owned-biopharmaceutical company in ASEAN. Two located in Myanmar are Insein and Yarthargyi. They are state-owned companies and are considered as emerging vaccine manufacturers in ASEAN and belonged to Myanmar pharmaceutical industry under the Ministry of Industry.

In Singapore, the GSK manufactures active ingredients of PCV in bulk as described earlier. Both public and private representing five (5) vaccine manufacturers are noted apparently in Thailand i.e. 1) Government Pharmaceutical Organization (GPO) acted as a government enterprise under the Ministry of Public Health, 2) Queen Saovabha Memorial Institute (QSMI) acted as a public sector, 3) GPO-Merieux Biological Products (GPO-MBP); a joint venture company partnering between the GPO and Sanofi Pasteur, France, 4) BioNet ASIA and 5) Greater Pharma. The latter two are private vaccine manufacturer companies producing some vaccines in place.

Lastly, Viet Nam has four (4) vaccine manufacturers which include 1) The Company for Vaccine and Biological Production No.1 (VABIOTECH), 2) The Center for Research and Production of Vaccines and Biology (POLYVAC), 3) The Institute of Vaccines and Medical Biologicals (IVAC) and 4) The Dalat Pasteur Vaccines Company Limited (DAVAC). All are state-owned vaccine production company under the supervision of the Ministry of Health.

Interestingly, other private Saudi vaccine manufacturers such as AJ Biologics invested in vaccine industry and commercialized to Malaysia and other ASEAN countries. In the recent past, AJ Biologics announced a plan to construct a vaccine manufacturing facility in Bandar Enstek, Negri Sembilan in Malaysia to make itself a key industry player in regional and global vaccine markets. This will also allow Malaysia to be recognized as a new vaccine producing country in ASEAN, tentatively by 2020-2022.

3.2 Vaccine product lists

In production area and as recommended by the WHO position paper for 2018, vaccine products for routine and non-routine immunisation programmes have been classified by manufacturers. List of products and names of manufacturer are shown in Figure 1 and Figure 2.

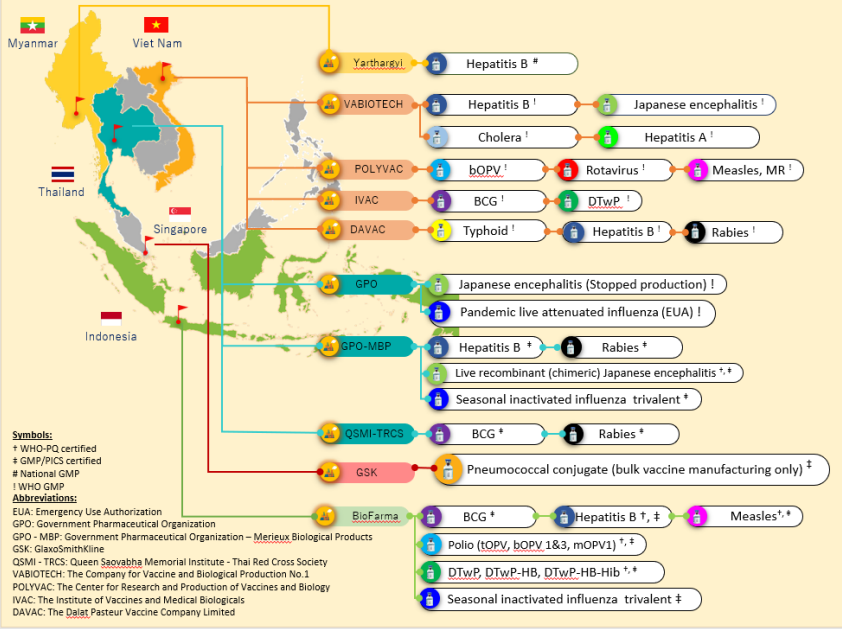

Fig 1 Production capacity of routine EPI vaccines among vaccine producing AMS

Based on Fig 1, it is shown that up to 16 antigens representing 18 vaccine products can be produced by manufacturers within the region to support routine immunisation programme recommended by the WHO position paper for 2018 (except conjugated bulk vaccine of Pneumococcal as described previously). They are:1) Hepatitis B virus (HBV), 2) *Japanese encephalitis*, 3) *Vibrio cholerae* (VC), 4) Hepatitis A virus (HAV), 5) Polio virus, 6) Rotavirus, 7) Measles virus, 8) Rubella virus, 9) *Mycobacterium tuberculosis*, 10) *Corynebacterium diphtheriae*, 11) *Clostridium tetani*, 12) *Bordetella pertussis*, 13) *Haemophilus influenzae* type B (Hib), 14) *Salmonella typhi*, 15) Rabies virus and 16) Influenza virus.

The 18 vaccine products available in relation to 16 antigens are: 1) HB vaccine, 2) inactivated sucking mouse brain (SMB) JE, 3) live recombinant (chimeric) JE, 4) Cholera vaccine, 5) HA vaccine, 6) trivalent Oral Poilovirus Vaccine 1-3 (OPV), 7) bivalent OPV 1&3, 8) monovalent OPV1, 9) Rotavirus vaccine, Measles containing vaccines i.e. 10) Measles vaccine; 11) Measles-Rubella (MR) vaccine, 12) Bacilli Calmette-Guerin (BCG), DTP containing vaccines i.e. 13) Diphtheria Tetanus and Pertussis (DTP); 14) DTP-HB; 15) DTP-HB-Hib, 16) Typhoid vaccine, 17) Rabies vaccine and 18) seasonal inactivated influenza vaccine (trivalent).

In addition, a specific vaccine like pandemic live-attenuated influenza H1N1 was also produced by the Thai GPO in close cooperation with the Faculty of Pharmacy, Silpakorn University as a pilot plant. This vaccine was approved locally for Emergency Use Authorization (EUA) only. To date, production of sucking mouse brain was stopped; JE was inactivated by the Thai GPO due to safety reasons. Currently, production of JE vaccine has shifted towards a novel cell-based culture technology and both GPO of Thailand and VABIOTECH of Viet Nam are working hard on this new technology replacement.

In the near future, a viral vaccine for protection against cervical cancer caused by Human Papilloma Virus (HPV) serotype 16 and 18 will be manufacturing by the GPO-MBP, under a Memorandum of Agreement (MOA) made between Xiamen Innovax Biotech, China (disclosing party) and GPO-MBP, Thailand (receiving party) for technology transfer. The Production process of this vaccine is considered as down-stream using a fill-finish, final bulk of HPV, and the licensed product is expected to be launched by 2021.

3.3 Vaccine production processes and product quality control

In terms of production processes and product quality control, it was found that nearly all of vaccines manufactured in Indonesia, Myanmar, Singapore and Viet Nam involve upstream processing. Except for Influenza and HB vaccines manufactured by the PT BioFarma (Indonesia) and with HB and Rabies vaccines manufactured by DAVAC (Viet Nam), their production process is characterized as downstream. In contrast, nearly all vaccines manufactured in Thailand mainly use downstream processing even the live recombinant (chimeric) JE vaccine domestically produced by the GPO-MBP. Three vaccines clearly noted as upstream production in Thailand are BCG, aP and Tdap. The first is manufactured by the QSMI-TRCS and the last two are manufactured by the BioNet ASIA.

Multi-level vaccine production quality was documented in vaccine producing AMS. Most vaccine products manufactured by the PT BioFarma (Indonesia) have been prequalified by the WHO (WHO prequalification; WHO-PQ), except trivalent Influenza and HB vaccines which has received only an international standard of Good Manufacturing Practice – Pharmaceutical Inspection Co-operation Scheme (GMP-PICS). The significance of having WHO-PQ is that prequalified vaccines can be exported internationally and especially supplied to United Nations procurement agencies i.e. United Nations Children's Fund (UNICEF), Gavi; the Vaccine Alliance and Pan American Health Organization (PAHO) Revolving Fund.

For two (2) vaccine manufacturers (Insein and Yarthargyi) in Myanmar, their production processes comply only with national GMP, rendering two kinds of vaccine produced (TT and HB vaccines) to be sold and used restrictively within the country and targeting mainly adults in the private health sectors and troops. Furthermore, introduction of these vaccines to the NIP is still questionable in terms of quality and safety issues owing to the lack of an effective monitoring and report systems for Adverse Events Following Immunisation (AEFI). Given the production capacity of TT is quite limited, Insein can supply approximately 10-20% of this vaccine to the country and the rest (80-90%) is imported. However, Insein is currently encountering big challenges on conventional technology for TT production using a Harvard strain dedicated by India. This strain provides a low number of production yield and technical

assistance from India can no longer be relied on in the future. In terms of HB vaccine, its production started from 2007 by the Yarthargyi under a technology-transfer project launched by South Korea.

In Thailand, all vaccines produced comply with GMP-PICS guidelines as the National Regulatory Authority (NRA) (currently known as Thai Food and Drug Administration or FDA) is a member of GMP-PICS. However, the predominant live recombinant (chimeric) JE manufactured by the GPO-MBP is only one vaccine that has been prequalified by the WHO and exported to several countries in the world. Whereas all vaccines produced in Viet Nam have complied to the WHO-cGMP (current GMP) standards as the Drug Administration of Viet Nam (DAV) was recently certified by the WHO for a fully-equipped NRA system in 2015. It is important to note that, POLYVAC by Viet Nam is the fourth vaccine manufacturer in Asia to produce the MR vaccine following Japan, India and China, under a technology-transfer project launched by the Japan International Co-operation Agency (JICA)[9]. At the same time, the POLYVAC is also a leading company in ASEAN region that successfully developed and produced the Rotavirus vaccine.

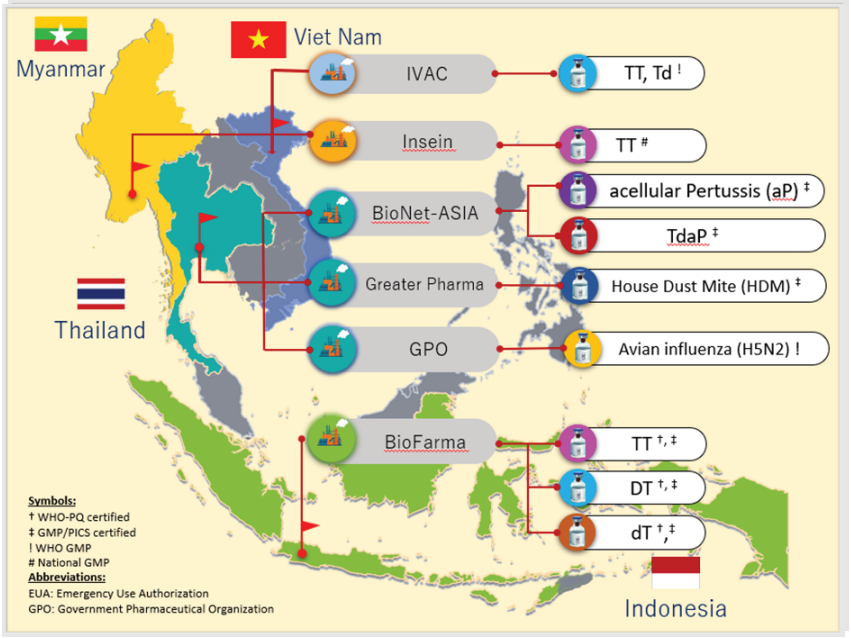

Fig 2 Production capacity of non-routine EPI vaccines among vaccine producing AMS

For non-routine EPI vaccines, seven (7) vaccine products are apparently noted to be manufactured by six (6) vaccine manufacturers and distributed in four (4) vaccine producing AMS i.e. Indonesia, Myanmar, Thailand and Viet Nam as shown in Figure 2. Based on current evidences, it is clearly claimed that production process of seven (7) vaccines have been considered as upstream processing. In brief, all three (3) vaccines produced by the PT BioFarma included TT, Diphtheria Tetanus (DT) and Tetanus diphtheria (Td).

They have been prequalified by the WHO to ensure product quality and safety. One vaccine produced by Insein, Myanmar is TT, more details have been described previously. In Thailand, 2 private vaccine companies manufactured different three (3) kinds of vaccines i.e. a single acellular Pertussis (aP), Tetanus diphtheria acellular Pertussis (TdaP) by BioNet ASIA and House Dust Mite (HDM) vaccine by Greater Pharmafor prevention of allergic diseases. An additional vaccine produced by the GPO is the live-attenuated Avian influenza H5N2. This vaccine was approved to be use only under certain outbreaks or pandemic. In part of product quality, vaccines from two (2) private companies and the GPO have been certified for GMP-PICS guidelines and WHO-cGMP standards, respectively. The production process of two (2) vaccines (TT and Td) produced by POLYVAC also strictly comply with to WHO-cGMP standards.

Irrespective of vaccines, other biopharmaceutical products such as snake antivenom, Tetanus Antitoxin (TAT) and Diphtheria Antitoxin (DAT) are also being produced by some vaccine manufacturers in ASEAN. In brief, at least three (3) vaccine manufacturers have current capacity to produce snake antivenom which include the PT BioFarma, QSMI-TRCS and Research Institute for Tropical Medicine (RITM). Moreover, the PT BioFarma also took efforts in producing DAT. For TAT, it could be produced by both the PT BioFarma and Insein. In the past 6 years, Insein had produced DTP and Rabies vaccine production; the production of these vaccines was terminated in 2013 due to frequently reported AEFI after vaccination. In the same way up to 8-kind of vaccines (Small pox, Cholera, Typhoid, Diphtheria, Pertussis, Tetanus, BCG and JE) could be produced by the GPO of Thailand. But with high requirement of product quality control, particularly GMP compliance required by global health partners, huge development of production process resulted at country level. Unfortunately, this has led to unexpected consequences in production disruption and failure to present.

It should be noted that currently there are only around one (1) to five (5) existing vaccine manufacturers in each of the vaccine-producing AMS. The low number of manufacturers working on the same product may have substantial influence on price competitiveness of vaccines in the market. Additionally, types and volume of vaccines produced in ASEAN may or may not match well with the AMS' collective vaccine demand specified in their National Immunisation Programs (NIPs). Regional policy mechanism to ensure a good balance between the production (supply) side and the collective national demand needs to be urgently formulated in the region so that AVSSR could be monitored and ensured in the long run.

3.4 National policy on vaccine development and production

Based on information obtained in country expert interviews and study visits to potential ASEAN vaccine manufacturers, it was revealed that firm political will and commitment on vaccine production for national security and self-reliance are key success factors that contributed to clear directives on vaccine R&D to meet the needs of each country.

Among vaccine producing AMS, Indonesia and Viet Nam are good examples and sources of beneficial lessons that can be learned by other AMS on this area. In brief, Indonesia has strong policy commitment on vaccine development and production as the most basic vaccines scheduled in the National Immunisation Programme (NIP) have been locally

produced and supplied for the country by the PT BioFarma. There are only some routine Expanded Programme on Immunisation (EPI) vaccines imported from multifunctional companies.

For Viet Nam, it provides evidence on National Product Lists (NPL) for vaccine R&D (medicine included). Under the co-implementation of the Ministry of Health (MOH) and Ministry of Science and Technology (MOST), they have defined a list of essential vaccines that meet the country's , and have incorporated them into the NPLL, and is then submitted to the cabinet for approval. Thereafter, all activities regarding targeted vaccine R&D will be supported and funded directly by the government. In other words, it should be said that Viet Nam has the best case of self-manufacturing of essential vaccines for national security priority in ASEAN as all vaccines produced domestically are used in the national EPI.

4. National regulatory capacity profile

According to the National Regulatory Authorities (NRA) assessment by WHO, many of the AMS seem to have sufficient capacity. However, some AMS lack essential capacity to perform a few national regulatory functions, given that standard requirements are different between vaccine producing and non-vaccine producing countries, especially those related to laboratory access, lot release and clinical trials (see Table 8 and Table 9).

In general, all six (6) critical control functions and one (1) system postulated by the WHO in ensuring quality and safety of vaccines should be exercised completely among vaccine producing countries. It was found that there are only three (3) out of five (5) vaccine producing countries in ASEAN i.e. Indonesia, Thailand and Viet Nam can fulfill the entire function of National Regulatory Authorities (NRA). In Myanmar and Singapore, some essential functions related to post marketing surveillance and system of lot release are missing, respectively.

Regarding A-3 leading vaccine producing countries namely, Indonesia, Thailand, Viet Nam, and Singapore, have also been members of ASEAN harmonization schemes and the highest international standard GMP/PICS. Basically, the initiative of ASEAN harmonization schemes are composed of two important activities which include 1) ASEAN Common Technical Dossier (ACTD) and 2) ASEAN Technical Requirements (ACTR). As indicated in Table 8 and Table 9, the requirement in establishing National Regulatory Systems (NRS) has been accomplished by vaccine producing and non-vaccine producing countries. Several national bodies have taken their roles and responsibilities on NRA and National Control Laboratory (NCL), except Cambodia.

For NRA assessment conducted by the WHO, it was found that four (4) out of five (5) vaccine producing countries i.e. Indonesia, Myanmar, Thailand and Viet Nam have ever been evaluated for NRA capacity, except Singapore. The NRA re-assessment has been performed in both Viet Nam and Thailand in 2017 and 2018, respectively.

Among non-vaccine producing AMS, the Philippines is only one country that was able to accomplish a fully functioning NRA followed by Malaysia with some functions related to laboratory access lacking. In addition, at least two functions (marketing authority and post marketing surveillance) can be exercised by Brunei Darussalam, Cambodia and Lao PDR.

This is in relation to current status of the country on vaccine provision and procurement since, these critical control functions are dependent upon the source of vaccines.

For this reason, Cambodia and Lao PDR, including Myanmar have been classified as a group of countries that purchased EPI vaccines through the procurement mechanisms of United Nations (UN) like the United Nations Children's Fund Supply Division (UNICEF SD)

Table 8 Current capacity on the National Regulatory Authorities (NRA) in vaccine producing AMS

ASEAN countries	National Regulatory Systems (NRS)	Legal agencies responsible for the NRSs		Current active functions of 6 critical control for regulatory systems						NRA assessment by the WHO	Membership of ASEAN harmonization schemes	Membership of GMP/PICS
		National body for NRA	National body for NCL	Marketing authority (licensing)	Post marketing surveillance (pharmacovigilance)	System of lot release	Laboratory access (testing)	GMPs inspection	Clinical trial			
Indonesia	+	National Agency of Drug and Food Control (NADFC)		+	+	+	+	+	+	+	+	+
Myanmar	+	Department of Food and Drug Administration, Ministry of Health and Sports	N/A	+	-	+	+	+	+	+	-	-
Singapore	+	Health Sciences Authority (HSA)	N/A	+	+	-	+	+	+	-	+	+
Thailand	+	1. Food and Drug Administration (FDA); 2. Bureau of Epidemiology (BOE), Department of Disease Control, Ministry of Public Health	3. Department of Medical Sciences (DMSC), Ministry of Public Health	+	+	+	+	+	+	+ (Re-NRA assessment in 2018)	+	+
Viet Nam	+	1. Drug Administration of Vietnam (DAV); 2. Administration of Science - Technology and Training (ASTT); 3. General Department of Preventive Medicine (GDPM); 4. National Institute for control of vaccine and Biologics (NICVB), Ministry of Health	National Institute for control of vaccine and Biologics (NICVB)	+	+	+	+	+	+	+ (2017)	+	+

Symbols:
+ : Presence of essential regulatory functions
- : Absence of essential regulatory functions

Table 9 Current capacity on the National Regulatory Authorities (NRA) in non-vaccine producing AMS

ASEAN countries	National Regulatory Systems (NRS)	Legal agencies responsible for the NRSs		Current active functions of 6 critical control for regulatory systems						NRA assessment by the WHO	Membership of ASEAN harmonization schemes	Membership of GMP/PICS
		National body for NRA	National body for NCL	Marketing authority (licensing)	Post marketing surveillance (pharmacovigilance)	System of lot release	Laboratory access (testing)	GMPs inspection	Clinical trial			
Brunei Darussalam	+	Brunei Darussalam Medicines Control Authority	Scientific Services, Ministry of Health	+	+	-	-	+	-	-	+	-
Cambodia	N/A	N/A	N/A	+	+	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lao PDR	+	Food and Drug Department	N/A	+	+	-	-	-	-	+ (2015 and 2017)	+	-
Malaysia	+	National Pharmaceutical Regulatory Agency (NPRA)		+	+	+	-	+	+	+ (Pre-NRA assessment in 2014)	+	+
Philippines	+	Food and Drug Administration-Center for Drug Regulation & Research (FDA-CDRR)	Food and Drug Administration-Common Services Laboratory (FDA-CSL)	+	+	+	+	+	+	N/A	+	N/A

Therefore, at least two (2) functions of marketing authority and post marketing surveillance should be intensively exercised by this group (Table 9). Up to four (4) functions based upon the existing sorts of the UN procurement plus two (2) additional functions of system of lot release and laboratory access should be accomplished by Brunei Darussalam as it was classified as a self-procuring country for vaccines used in the national EPI.

It should be noted that nearly all of non-vaccine producing AMS are members of ASEAN harmonization schemes based on available information, except Cambodia. Malaysia is the only country among non-vaccine producing AMS to be a member of GMP/PICS even though it has no local vaccine manufacturer identified. The assessment of NRA capacity by the WHO was documented in two (2) out of five (5) non-vaccine producing AMS i.e. Lao PDR in 2017 and Malaysia in the pre-NRA assessment in 2014 (Table 9).

4.1 Regulatory requirement for vaccines

Regarding 10 AMS, there is no information to trace which regulatory requirements for vaccines are currently mandated by each AMS. However, based on information derived from study visit to the Drug Administration of Viet Nam (DAV), the team was informed that conduct clinical trials for all imported vaccines intended to be sold in Viet Nam must be done in Viet Nam. This intervention is considered a non-tariff barrier which aims to protect local vaccine manufacturers and industry from multifunctional companies. Moreover, the following are other compelled regulatory requirements in some countries in the world: a) need to have vaccine manufacturer's representatives in distributing countries and vaccine-prequalified by WHO; b) to have no less than18 months of vaccine shelf life; and c) to have an agreement on technology transfer on imported vaccines to local vaccine manufacturers.

5. National Immunisation Program (NIP) capacity profile

5.1 Vaccines and ASEAN immunisation schedules

As shown in Table 10, there are not more than 10 to 15 vaccines listed in the NIP of each AMS and are needed to be adequate supply all year round to effectively run their NIP. Hence, these products collectively should form the common vaccine products for the AVSSR. A list of "regional essential vaccines" should be developed and used for monitoring by the region and by each AMS alike to ensure that adequate supply of these vaccines would be maintained according to the need of AMS at all times. This is to increase the regional and country health security in ASEAN.

Table 10 Type of vaccines currently in use and in pipeline for the NIP introduction among AMS

Type of routine EPI vaccines	ASEAN countries									
	Brunei Darussalam	Cambodia	Indonesia	Lao PDR	Malaysia	Myanmar	Philippines	Singapore	Thailand	Viet Nam
1. WHO recommendations for all immunization programmes										
1.1 BCG	√	√	√	√	√	√	√	√	√	√
1.2 Hepatitis B	√	√	√	√	√	√	√	√	√	√
1.3 Polio (OPV/IPV)	√ (IPV)	√ (bOPV/IPV)	√ (bOPV/IPV)	√ (bOPV/IPV)	√ (IPV)	√ (bOPV/IPV)	√ (bOPV/IPV)	√ (bOPV/IPV)	√ (bOPV/IPV)	√ (bOPV)
1.4 DTP containing vaccine	√ (aP)	√ (wP)	√ (wP)	√ (wP)	√ (aP)	√	√ (wP)	√ (aP)	√ (wP)	√ (wP)
1.5 Haemophilus influenzae type B	√	√	√	√	√	√	√	√		√
1.6 Pneumococcal (conjugate)		√ (PCV-13)	√	√		√ (PCV-10)	√	√ (PCV-13)		
1.7 Rotavirus							√		√	
1.8 Measles	√	√	√	√	√	√	√	√	√	√
1.9 Rubella	√	√	√	√	√	√	√	√	√	√
1.10 Human Papilloma Virus (HPV)	√	√	√	√	√		√		√	
2. WHO recommendations for certain regions										
2.1 Japanese encephalitis		√	√	√	√	√			√	√
2.2 Yellow fever										
2.3 Tick-borne encephalitis										
3. WHO recommendations for some high-risk populations										
3.1 Typhoid					√					√
3.2 Cholera					√					√
3.3 Meningococcal					√					
3.4 Hepatitis A										
3.5 Rabies										
3.6 Dengue (CYD-TDV)							√			
4. WHO recommendations for immunization programmes with certain characteristics										
4.1 Mumps	√				√		√	√	√	
4.2 Seasonal influenza (inactivated tri-and quadri-valent)									√	
4.2 Varicella										

Remarks: : Demonstration project is underway

: NIP introduction is planned

Regarding Table 10, it shows that most essential vaccines for routine immunisation recommended by the WHO have been introduced to the National Immunisation Programme (NIP) of each ASEAN Member State. This is mainly based on their epidemiological patterns of communicable or infectious diseases and available national budget. According to the WHO position papers for 2018, these vaccines are characterized into four (4) groups :1) vaccines for all immunisation program, 2) vaccines for certain regions, 3) vaccines for some high-risk populations, and 4) vaccine for certain characteristics, respectively.

In addition, some new vaccines have been considering for further introduction to the Expanded Programme on Immunisation (EPI) by different AMS such as Human Papilloma Virus (HPV), Pneumococcus Conjugate Vaccine (PCV), live *Japanese encephalitis* (JE), and Rotavirus.

In brief, the pilot project of a two-dose HPV vaccinated at 9 years of female elementary school children is being demonstrated in six (6) operational districts of Cambodia and Jakarta in Indonesia, the same series of HPV vaccination demonstration is also underway in all female students grade 5 and 6 since 2016.

Moreover, the other two- pilot projects being run in Indonesia included PCV and live JE. A3-dose PCV is currently undergoing demonstration in 2 districts of Lombok, as well as a2-dose live JE vaccination in Bali as supported by the Gavi, the Vaccine Alliance since 2017. With regard to Malaysia, 2-dose live JE vaccination is being demonstrated in Sarawak region. Whereas, some particular vaccines i.e. Typhoid has been administered specifically among food handlers as a group of high risk population; Meningococcal and Cholera have been administered regularly in the outbreak areas of Sabah, Malaysia. The routine immunisation of Typhoid and Cholera vaccines are also observed in Viet Nam.

In Thailand, a 2-year demonstration project on Rotavirus vaccine was completed in two northern provinces of Sukhothai and Phetchabun since 2013. After the project, vaccination with this vaccine is still continuing in these two provinces as part of the EPI for children aged less than one year with the support of the Department of Disease Control, Ministry of Public Health.Currently, policy advocacy for introduction of Rotavirus vaccine to the NIP is in process. On the other hand, *Haemophilus influenzae* type B (Hib) in the form of pentavalent DTwP-HB-Hib is planned to be introduced as an addition to the NIP by 2019 to replace the existing tetravalent DTwP-HB. This is similar in Viet Nam, if Rotavirus vaccine can be produced adequately by the POLYVAC, a domestic vaccine manufacturer, it might be expanded and further introduced to the NIP for nationwide vaccination.

5.2 Vaccine procurement, management and logistics

An overview of vaccine procurement, management and logistics among AMS is shown in Table 11. Several facets of demand forecasting units, national purchasing bodies, budget systems for vaccine procurement, source of vaccines and logistics system will be accommodated in line with different groups of vaccine and non-vaccine producing AMS.

Table 11 Vaccine procurement, management and logistics among AMS

ASEAN countries	Estimated annual birth cohort	Vaccine demand forecasting unit	Vaccine procurement operation		Budget for vaccine procurement			Budget system for vaccine procurement		Source of vaccine procured		Vaccine logistics and distribution system	
			National procurement agency	Eligible country for GAVI support or UN agencies donation	Annual government budget	Sin tax	Single year	Multi-year contract	Domestic vaccine manufacturer	International vaccine manufacturer	Govt.	Private company
Vaccine producing AMSs												
Indonesia	4,818,211	EPI	Phamacy Unit (Directorate of Public Medice and Medical Device)	√ (in process of Gavi transitioning out Gavi support)	√		√ [Co-financing for new vaccines (Pentavalent, [PV, MR, JE)]		√		√	
Myanmar	1,017,043	Central EPI	Division of vaccine procurement, Department of Publich Health, MOHSs	√ (GAVI/ UNICEF)	√		√			√		√ (only Central to State and Regional level by Nandar Shwe Yi Company)
Singapore	41,000	Group Procurement Office (GPO) for the public sector; pharmaceutical companies also forecast vaccine demand.	Group Procurement Office (GPO) for public sector		√			√		√		√ [Supported by various third party logistics provider (e.g. Zuellig Pharma, ST Logistics, DKSH)]
Thailand	733,014	National Health Security Office (NHSO)	Ratchavithi Hospital on behalf of the Ministry of Public Health, Thailand		√		√ (By law)		√	√		√
Viet Nam	1,577,000	National Institute of Hygiene and Epidemiology (NIHE), Ministry of Health	NIHE	√	√			√	√	√	N/A	N/A
Non-vaccine producing AMSs												
Brunei Darussalam	6,451	1. Department of Community Health Services 2. Department of Public Health Services 3. Department of Pharmaceutical Services	Pharmaceutical Procurement, Department of Pharmaceutical Services		√		√	√		√	√ [State Medical Store, Procurement Division, Ministry of Health (for distribution from store to public health facilities)]	√
Cambodia	357,484	National Immunization Program	UNICEF	√	√		√			√	√ (National Immunization Program)	
Lao PDR	181,700	NP and UNICEF	UNICEF	√ (GAVI, JCV)	√		√ (JCV)			√	√	
Malaysia	508,203 (2016)	1. Disease Control Division, 2. Family Health Development Division, 3. Pharmaceutical Supply Unit for Public Health	Procurement Division, MoH		√	√	√	√		√		√ (3 major pharmaceutical logistic companies)
Philippines	2,399,000	N/A	N/A			√	N/A	N/A		√	N/A	N/A

In 10 ASEAN countries, different national bodies authorities have been in charge of annual vaccine demand forecasting and procurement and is addressed by top 5 countries with the highest estimated annual birth cohorts i.e. Indonesia (4,818,211), the Philippines (2,399,000), Viet Nam (1,577,000), Myanmar (1,017,043) and Thailand (733,014). Among 10 AMS, it is found that at least five (5) countries, namely Indonesia, Myanmar, Viet Nam, Cambodia and Lao PDR are eligible for new vaccines support by Gavi, the Vaccine Alliance. However, some of them are now in preparatory transition phase (2017-2020) of graduating from Gavi's support and to fully self-finance in 2021-2025 to promote country ownership on national EPI.

For example, Viet Nam will be graduating from pentavalent DTwP-HB-Hib vaccine support in 2019 whereas some countries like Indonesia and Myanmar are to start co-financing for new vaccines (i.e. pentavalent, IPV, MR, JE, PCV) as requested by the Gavi. Specifically, some vaccines used in Myanmar e.g. JE has also been funded by other UN agencies like the Program for Appropriate Technology in Health (PATH) than Gavi as well as the Japan Committee for Vaccine (JCV) funded the budget together with Gavi for vaccine supply in Lao PDR. In Gavi-eligible countries, all WHO-prequalified vaccines used in the NIP or only some particular vaccines will be purchased through the mechanisms of UNICEFSD, as a good partnership of the Gavi. However, Philippines as a self-procuring country has procured some vaccines with no suppliers in the country through the mechanisms of UNICEF SD.

Regarding national budgetary systems, it was found that most budget for vaccine procurement is allocated annually by nine central governments of AMS, according to their national budgetary systems confined by laws, except Philippines. Notably, there are only two AMS i.e. Malaysia and the Philippines revealed their main budget for vaccine procurement derived from the sin taxes, a taxation collected from harmful products that impact directly to people's health. For vaccine procurement, both systems, either single or multi-year contract, have been used by different AMS. In brief, a single year contract applied explicitly by five (5) AMS including Indonesia, Myanmar, Thailand, Cambodia and Lao PDR. Meanwhile a multi-year contract is applied by Singapore and Viet Nam. Interestingly, both system implementations have been noted in Brunei Darussalam and Malaysia as other self-procuring countries in ASEAN.

Theoretically, for some ASEAN countries like Cambodia, Lao PRD and Myanmar, their routine EPI vaccines are purchased fully through the mechanisms of UNICEF SD. Hence, it is surprising a single year contract for vaccine procurement stated in these countries. Indeed, a usual mechanism for vaccine procurement deployed by the UNICEF SD is a multi-year contract. Regarding the source of vaccine procured, local vaccine manufacturers are the main source of vaccines among vaccine producing AMS i.e. Indonesia, Thailand and Viet Nam. Except for Myanmar, all vaccines used in the NIP are imported from multifunctional companies owing to quality concerns on local vaccine production.

In terms of vaccine logistics and distribution system, either public or private transportation agencies have been used among AMS. It is found that the national vaccine procurement agencies of Cambodia, Indonesia and Lao PDR will take an additional role in distribution of vaccines. In contrast, other private transportation agencies have been out sourced in Myanmar, Malaysia, Singapore and Thailand. For instance, three pharmaceutical logistics companies in Malaysia, and various third-party logistics providers e.g. Zuelig Pharma, ST Logistics, DKSH in Singapore are being used. The use of both types of transportation agencies for vaccine logistics and distribution was clearly identified in Brunei Darussalam.

5.3 Mechanisms for new vaccine introduction

Based on available information obtained from the AVBS survey template. It was revealed that crude national mechanisms used for decision making on new vaccine introduction in the NIP is quite different and varied from country to country as described below:

Brunei Darussalam–the request for new vaccine introduction in the NIP requires a proposal which is then submitted to the Ministry of Health's National Committee on Extended Programme for Immunisation

Indonesia - 1. Several new vaccines, which include IPV, Rubella, JE, HPV, pneumococcus, are being introduced in the comprehensive Multi-Year Plan (cMYP) 2015-2019. The cMYP describes the strategies in order to achieve national and global targets and has included the introduction of new vaccines in the NIP as recommendedin the Global Vaccine Action Plan (GVAP)

2. New vaccine introduction in the NIP happens after the recommendation from the Indonesian Technical Advisory Group on Immunisation (ITAGI) has been approved based on scientific considerations (e.g. Cost Effectiveness Analysis (CEA), vaccine availability, sustainability financing, etc.)

3. National policy for vaccine and other logistics procurement is in place through one gate policy under the Pharmaceutical unit using the e-catalogue mechanism.

Lao PDR - New vaccine introduction in the NIP is approved by the National Immunisation Technical Advisory Groups (NITAGs) and then submitted to MOH.

Malaysia –A proposal for new vaccine introduction in the NIP is submitted to the National Committee on Immunisation Practices (NCIP) for discussion and approval. Subsequently, funds for vaccine purchasing will be requested from the Ministry of Finance.

Myanmar - New vaccine introduction in the NIP is supported by Gavi the Vaccine Alliance through procurement mechanisms of the UNICEF SD. Myanmar Central Expanded Programme on Immunisation (CEPI) and other partners according to the NITAG are in charge of the NIP implementation under supervision of the Ministry of Health and Sports (MOHS).

Singapore - The MOH in consultation with the Ministry's Expert Committee on Immunisation reviews vaccines for introduction in the NIP. The following criteria are considered:

- Burden of disease
- Vaccine safety and efficacy
- Cost-effectiveness

Thailand –A list of new vaccines for introduction in the NIP is recommended by the Advisory Committee on Immunisation Practices (ACIP). At least 2 sub-committees [Health Promotion and Disease Control and National Essential Drugs List (NEDL)] will scrutinize and make decision based upon scientific information (i.e. burden of diseases, severity of diseases, vaccine safety and efficacy and CEA). Other criteria taken in to consideration are equity and

budget sustainability. After approval, budget for vaccine purchasing requested by the National Health Security Office (NHSO) will be submitted to the Ministry of Finance.

From information above, an equivalent body of NITAGs as suggested by the WHO plays a crucial role in prioritizing and giving recommendation on which kind of vaccines should be introduced in the NIP. However, throughout the processes for new vaccine introduction, it was found that the process takes a longer time, commonly not less than 10 years for introduction of one new vaccine. As observed by Indonesia and Thailand. So, the current challenge is how to shorten or streamline the process keeping with effective deliberation, in order to accelerate the introduction of new vaccines in the NIP to ensure people will be able to timely and equitable access to quality vaccines.

5.4 National policies and strategies in support of vaccine security and self-reliance

A set of policies and strategies in ensuring vaccine security and self-reliance have been implementing differently among vaccine and non-vaccine producing AMS as described in Table 12 and 13.

By definition, vaccine security is mainly to guarantee a sufficient supply of affordable, safe and quality vaccines to be used both in regular and emergency situations. Practically, several key activities in fostering vaccine security can be generalized through an effective planning of vaccine supply chain management e.g. long-term and accurate forecasting of vaccine demands, long-term budget allocation for vaccine purchasing, pooled procurement, multi-year contract, multi-suppliers, stockpiling, etc. In contrast, the word of “self-reliance” means a self-production of essential vaccines used in the NIP should be established domestically at country level to assure sustainable supply of vaccines in the long run.

Taken together, the conclusive definition of the AVSSR is to enhance an effective management of vaccine supply chain and promote self-production of essential vaccines to assure the availability of affordable, safe and quality vaccines to be used both in regular and emergency situations among AMS.

Table 12 National policies and strategies in support of vaccine security and self-reliance among vaccine producing AMS

ASEAN contries	National policies	National strategies
Indonesia	N/A	N/A
Myanmar	Childhood immunization is an intregral part of the basic Essential Package of Health Services (EPHS) under the National Health Plan for 2017-2021	- Five years commitment for vaccine financing - Vaccine Independence Initiative (VII) plan is approved and commited by the cabinet (2017-2020) - MOU between MOHSs and UNICEF SD - Fund Act to garautee finacial buffer between vaccines procured by the UNICEF SD and the payment by the government - Revolving fund offers key advantage on flexible credit terms with regard to the management of immunization finances
Singapore	N/A	N/A
Thailand	National vaccine policy and strategic plan	- Vaccine management (multi-year contract, pooled procurement, emergency vaccine stockpile) - Promote vaccine R&D, including production - Support local vaccine manufacturers (privilege) - Develop essential infrastructure, HRD and networks
Viet Nam	1. Natinal stratgy on development of the Veitnam pharmaceutical industry up to 2020, with a vision toward 2030 (2014)	1.1 Bring Viet Nam to play a potential role in development of vaccine production 1.2 Vaccines produced domestically shall meet 100% of demand for the EPI and 30% of demand for fee-based service immunization by 2020 1.3 Initiative in production of vaccines for epidemic prevention by 2030
	2. Pharmaceutical law, chapter 3 defines the state pharmaceutical policy and pharmaceutical industry development (2016)	2.1 Provide incentive for manufacturing of vaccines 2.2 Facilitate procedures for registration of WHO pre-qualified vaccines 2.3 Combine investment from state budget and other sources in development of vaccine manufacturers 2.4 Manufacture of vaccine is one prioritized fields in development of pharmaceutical industry

Table 13 National policies and strategies in support of vaccine security and self-reliance among non-vaccine producing AMS

ASEAN countries	National policies	National strategies
Brunei Darussalam	- National Medicine Policy encourages local production of medicines - Vaccination legislation as per listed in the Infectious Diseases Act 2010	- Due to limited capacity and technological know how, vaccine production may not be a priority at this moment - to attract Foreign Direct Investment (FDI) - Emergency fund allocated for pandemic situation - Stockpiling - Pre-qualification sources - Group purchasing
Cambodia	N/A	- A comprehensive multi-year plan for 2016-2020 for immunization programme, including costing - An annual operational plan with budget for approval from the Ministry of Health - Procure traditional vaccines and injecion supplies through UNICEF SD procurement services - Provide portion of funds (co-funding) for new vaccines - Provide funds for other immunization activities
Lao PDR	Immunization law	- Increase government invesment for vaccines and operational cost
Malaysia	National Medicines Policy (NMP) to ensure good mangement of medicines - 3rd core component: continuous access to medicines through efficient and intrgrated management and supply network	- Vaccine in the NIP procured through concession agreement/central contratcs - Concession agreement (Pharmaniaga Logistics) : Approved Product Purchase List (APPL) - 3-year tender cycle (currently 2017-2019) - Minimum 2-3 months buffer stocks kept at warehouse - Delivery of stocks within 7 working days (WM), 10 working days (EM) - Central Contract with agreed terms: e. g. estimated quantity, delivery of stocks within < 30 working days - Import of non-registered vaccines from alternative sources in special circumstances is exempt
Philippines	Vaccine Self Sufficiency Program (VSSP) is a priority program by the President of the Philippines cascaded to the Secretary of Health	Procure some vaccines with no suppliers in the country through UNICEF SD procurement services, under the Department of Health (DOH)'s management

6 Challenges and gap analysis

The list of most frequent and outstanding challenges and gap analysis statements based upon current capacity of each AMS on vaccine development, production, regulation and immunisation among AMS is shown in Table 14 through Table 17.

The statements were expressed by informants in the AVBS 2017 survey template and/or by experts or officials through other channels as described earlier. All statements need to be scrutinized further by concerned experts and officials responsible for the designated areas of vaccine value chain before real action could be taken to fill the gaps. Most of these statements were well taken and agreed on by participants of the AVSSR workshop 2018.The regional strategic and action plans for the AVSSR were formulated based on findings derived from challenges and gap analysis, amid the extensive discussion.

Table 14 Challenges and gap analysis on vaccine research and development among AMS

Vaccine research and development
1. Insufficient qualified staffs, skilled personnel, experts and bioinformaticians for vaccine development
2. Budget constraints
3. Lack of essential facilities, machineries, equipment, etc. for vaccine development
4. Lack of know-how for vaccine development
5. Lack of clear political policy and commitment in supporting vaccine research and development

Table 15 Challenges and gap analysis on vaccine production among AMS

Vaccine production
1. Lack of infrastures or facilities for manufacturing of potential vaccines
2. Lack of qualified staffs, skilled personnel and experts for vaccine production
3. Require high vaccine quality improvement to meet international standard i.e. WHO-PQ for exportation
4. High competitive market between vaccine produced locally and imported vaccines from multifunctional companies
5. Lack of promoting usage of vaccine produced domestically in the NIP/EPI
6. Lack of clear political policy in support of vaccine production for national security and self-reliance
7. Lack of firm support on vaccine production from the government
8. Survival of local vaccine manufacturers under limited budget allocation from the government
9. High turn-over rate of quilified staffs and appropriate measurements for retention

Table 16 Challenges and gap analysis on vaccine regulation among AMS

Vaccine quality control (regulation)
1. Limited capacity on quality control and testing of vaccines both equipment and human resources
2. Limited capacity of lot release, clinical trial, and pharmacovigilance
Limited capacity on vaccine dossier assement
3. Require new test methods for quality control of vaccines due to more new vaccines are registered
4. Limited capacity of developing potency test methods on identified vaccines for the purpose of post-marketing surveilance (PMS)
5. Difficulty of obtaining samples and reference standard materials from Market Authorisation Holder
6. Limited capacity on vaccine dossier assessment
7. Limited vaccine experts for dossier reviews
8. Limited knowledge of Quality Management System (QMS)
9. Limited budget for training, facility, and equipment

Table 17 Challenges and gap analysis on National Immunisation Programme (NIP) among AMS

National immunization programme (NIP)
1. Rely on supplies from international manufacturers; hence lead to high price of vaccines (cost per dose), uncontrolled logistics and timeline
2. In process of accelerated transitioning phase of graduating from the Gavi support for fully self-financing on vaccine procurement
3. Vaccine refusal at selected areas and countering vaccine hesitant groups (negative campaign, religion issues)
4. Limited budget for vaccine purchasing; hence lead to timely fund disbursement and clearance process
5. Cold chain control during transportation and storage, including infrastructure for expanded new cold chain equipments
6. Shortage of essentnial vaccines at national, regional and global levels
7. Discrepancy of Immunization coverage rate and how to maintain a high coverage rate of immunization
9. Data quality related to high drop-out rate
10. Discrepancy of vaccination schedule between public and private health sectors
Different geographical areas cause of difficulty to access vaccination services
11. Complexity of mechanisms for new vaccine introduction which lead to delayed introduction of essentail vaccines in the EPI
12. High turn-over rate of quilified staffs and require continuing capacity building

Conclusions:

Even though the AVBS 2017 results were based on data supplied by a small number of informants and with certain limitations arising from data collection methods, the given conclusions have been verified repeatedly with data and information from other sources. Results were found to be accurate and reliable enough especially for a start in the formulation of strategic and action plan for AVSSR.

Findings have confirmed that ASEAN has substantial resources and growth potential in all the four areas of vaccine value chain. These resources and potential are available in all the member states and it is fully possible to get more contribution and collaboration from all AMS to accelerate the vaccine development and production in this region. To achieve the

main objective of AVSSR that is the ensuring of sufficient supply of essential vaccines to be used in both regular and emergency situations in ASEAN, additional investment coupled with good strategies to strengthen the existing capacity and potentials in vaccine development and production of ASEAN as a whole should be urgently and carefully implemented.

In addition to solidarity among AMS, ASEAN needs to closely collaborate and foster the partnership with international development partners in vaccine development and production since the region is still vulnerable to VPD outbreaks, vaccine security is still an issue among AMS due to many reasons, and high level of technology is strongly needed to move further in vaccine development and production.

Finally, it would be very useful to conduct periodic follow-up surveys in order to monitor the degree of development that has occurred in all the four areas of vaccine value chain, Ideally to ensure that data would be more accurate and reliable than the survey this time, follow-up surveys on the regional and country capacity for vaccine production and development should be planned and conducted by a multi-country team consisting of representatives from all AMS in the spirit of one ASEAN community. Results from such an arrangement would be crucial in adjusting the strategies and actions to be taken so that AVSSR might be achieved sooner.

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