ISEAS YUSOF ISHAK INSTITUTE

ISSUE: 2022 No. 29
ISSN 2335-6677

PERSPECTIVE

RESEARCHERS AT ISEAS – YUSOF ISHAK INSTITUTE ANALYSE CURRENT EVENTS

Singapore | 21 March 2022

The Race to Produce Covid-19 Vaccines in Southeast Asia

*Tham Siew Yean**

People scan QR codes using the Trace Together contact tracing app on their smartphones before entering a building at the Raffles Place financial business district in Singapore on 14 February 2022. Picture: Roslan RAHMAN, AFP.

** Tham Siew Yean is Visiting Senior Fellow at ISEAS – Yusof Ishak Institute and Emeritus Professor, Universiti Kebangsaan Malaysia.* *She thanks Siwage D. Negara and Jayant Menon for useful comments. The usual caveat remains.*

ISSUE: 2022 No. 29
ISSN 2335-6677

EXECUTIVE SUMMARY

- The race to produce Covid-19 vaccines in SEA is triggered by a general reluctance to be dependent on the vagaries of global supply, imports and donations as well as uncertainty over the duration of the pandemic.
- Joining the exclusive vaccine production club will require Southeast Asian countries to enter the vaccine value chain of one of the key producers as contract manufacturers. Indonesia and Malaysia have collaborated with Sinovac, while Thailand has teamed up with AstraZeneca, with more partnerships in the offing.
- Some Southeast Asian countries such as Indonesia, Singapore, Thailand and Vietnam are also venturing into the production of home-made vaccines and these have already advanced to clinical trials with plans for these vaccines to be rolled out in 2022.
- But, there are numerous other vaccines that are being developed around the world that are also undergoing clinical trials. It remains to be seen whether Southeast Asia's home-made vaccines can compete with the new vaccines that are also coming on board as well as established vaccines, especially when trust in home-made vaccines remains low.
- It also remains an open question whether the future course of the pandemic may render vaccination and the use of home-made vaccines in Southeast Asia redundant or if the vaccines made in the region can combat new variants effectively.
- Be that as it may, the technology acquired in the vaccine development process in Southeast Asia can be used to prepare these countries for future pandemics.

ISSUE: 2022 No. 29
ISSN 2335-6677

INTRODUCTION

Vaccine inequity and protectionism continue to prevail despite the World Health Organisation (WHO)'s calls to the contrary. While high income countries may have seen 73 percent of their population completing their first protocol, lower middle-income countries have only attained 46 percent.[1] Low-income countries have a mere 7.9 percent, which is a far cry from WHO's targets of vaccinating 40 percent of the population of every country by the end of 2021 and 70 percent by the middle of 2022.[2]

One way of meeting vaccine inequity is to enable developing countries to produce their own vaccines. Sharing patented technology and knowledge with drug manufacturers can help to increase supply. However, this would require the current vaccine producers to temporarily waive their intellectual property right on the Covid-19 vaccines that they have developed. This has in fact been proposed by India and South Africa at a World Trade Organization meeting in October 2020, but unfortunately, action on this has since stalled.[3]

Nonetheless, the scramble for vaccines, in the face of uncertain supplies and uncertainty about the efficacy and longevity of current vaccines against new variants, has led some countries in Southeast Asia (SEA) to forge domestic production, be it with existing producers as sub-contractors, or independently. This is to ensure adequate supply for their own needs, reduce their dependency on imports as well as enhance their learning and capabilities to cope with future health pandemics.

PRODUCTION OF COVID-19 VACCINES IN SOUTHEAST ASIA

There are five stages in vaccine development and manufacturing (Table 1), with each step involving separate fixed costs. The exact cost of research and development (R&D) and the manufacture of vaccines are unknown due to lack of transparency among pharmaceutical companies.[4] The Coalition for Epidemic Preparedness Innovations, however, has estimated that the cost of developing a single epidemic infectious disease vaccine to be around USD 31 to 68 million, assuming no risk of failure.[5] Existing Covid-19 vaccine developers such as Pfizer/BioNTech and Moderna have reportedly received USD8.25 million in support in the form of public funding as well as guaranteed government pre-orders.

Besides funding, vaccine development and manufacturing also require R&D capabilities and capacities to develop vaccines from scratch. Thus, most developing countries may not have the research capacities as well as public/private financial support needed for Stage 1 of vaccine development.

The vaccines are then tested in three separate phases in clinical trials to ensure that they are safe and effective.

ISSUE: 2022 No. 29
ISSN 2335-6677

Manufacturing production is divided into three other stages, from drug substance and drug product formulation, to fill and finish, and later to distribution. Pharmaceutical companies have been shifting towards fragmentation due to the separability of fixed costs in each stage of vaccine development and manufacturing. Developing countries without R&D capabilities can therefore participate in vaccine manufacturing through contract manufacturing for Stages 3 to 5. In particular, scaling up production to meet with demands during the Covid-19 pandemic has led to the outsourcing of production in these three stages. For developing countries, manufacturing can facilitate technology transfer because the technology involved is not confined to the R&D stage alone but includes management of the entire production process. Manufacturing vaccines, including Covid-19 vaccines, require stringent regulatory oversight in the manufacturing process for safety reasons since these vaccines are provided for healthy individuals. Manufacturers have to demonstrate the ability to manufacture according to clear and documented procedures with reliable equipment and personnel, for an extended period of time, without failure or interruptions.

Table 1. Five Stages of Vaccine Development and Manufacturing

	Stages	**Requirements**
1	Research and Development (R&D)	R&D Capabilities
2	Clinical Trials	National Regulatory Agencies with approved protocols and ethics committee
3	Drug Substance and Formulation	Capital equipment, raw and single-use materials, and other pharmaceutical ingredients
4	Fill and Finish	Capital equipment and other inputs
5	Distribution	Range of equipment

Source: Adapted from Bown and Bollyky, 2021[6]

SEA Countries with Existing Vaccine Production Facilities

The ASEAN Vaccine Baseline Survey (AVBS) was conducted as part of the ASEAN Vaccine Security and Self-Reliance (AVSSR) initiative.[7] The Survey aimed to describe the 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.[8]

The Survey results were published in 2019, just before the onset of the Covid-19 pandemic and serve as a useful guide on the capacity of SEA countries in vaccine production in general. Based on the survey, SEA can be divided into two groups, namely vaccine-producing countries and non-vaccine producing countries. The former includes Indonesia, Myanmar, Thailand and Vietnam (Table 2), thereby indicating the possibility of these countries venturing into the production of Covid-19 vaccines.

ISSUE: 2022 No. 29
ISSN 2335-6677

Table 2. Current capacity on vaccine research and development in vaccine-producing AMS, as at 2019

Country	Capacity on R&D Research	Research Institute/Organisations
Indonesia	Yes	PT BioFarma
Myanmar	Yes	Department of Medical Research, Ministry of Health
Thailand	Yes	Government Pharmaceutical Organisation (GPO); Centre for Vaccine Development (CVD), Mahidol University Chiangmai University Vaccine Research Center, Chulalongkorn University National Science and Technology Development Agency (NSTA), Ministry of Science and Technology BioNet ASIA CVD and GPO Department of Medical Science (DOMS), Ministry of Public Health Siridhorn Institute of Technology (SIIT) National Biopharmaceutical Facility (NBF) and DOMS
Vietnam	Yes	VABIOTECH* The Centre for Research and Production of Vaccines and Biologicals (POLYVAC) Institute of Vaccines and Biological Medical (IVAC)

Note: * Name of State-Owned Company which used to belong to The National Institute of Hygiene and Epidemiology (NIHE);

Source: https://asean.org/wp-content/uploads/2021/10/Agd-6.3.a.i_AVBS_Final_23082019.pdf

ISSUE: 2022 No. 29
ISSN 2335-6677

Production with Existing Vaccine Producers

Given the facilities available for vaccine production as shown in Table 2, it is not surprising that Indonesia and Thailand moved quickly to collaborate with existing Covid-19 vaccine developers when the pandemic broke out in early 2020.[9] The Indonesian embassy in Beijing had sought to establish contact with Sinovac in March 2020. Three months after that, Sinovac agreed to cooperate with Bio Farma in conducting clinical trials as well as vaccine manufacturing. In August 2020, a phase-three clinical trial was carried out for Sinovac's vaccine. Under the agreement with China, Bio Farma of Indonesia acquired the license to produce CoronaVac and has been designated a production hub for the region. The company started to "fill and finish" 15 million CoronaVac doses for distribution from mid-January 2021, while Brazil is the other production site for the vaccine.

Thailand also negotiated for vaccine production, signing an advance agreement in November of 2020 to secure an undisclosed number of doses of the AstraZeneca/Oxford vaccine and authorization for local production by the Thai drug manufacturer Siam Bioscience, which had no prior experience in vaccine production.[10] It was then considered to be strategically important for Thailand to gain from technology transfer and to make the country self-reliant in vaccine production besides promoting and pushing the Thai pharmaceutical industry to the forefront in ASEAN.[11]

The deal was for Thailand to produce up to 200 million doses a year as the sole SEA production hub for this vaccine.[12] The Thai government had reserved about a third of those doses, with the rest bound for export to Indonesia, the Philippines, Vietnam and other neighbours.[13]

In June 2021, Siam Bioscience started the country's first production of a COVID-19 vaccine, using AstraZeneca's technology. However, teething problems led to a shortfall in the projected production, which affected the projected number of doses available for Thailand as well as the country's exports. The country has since emerged as a major manufacturer of the Oxford/AstraZeneca vaccine, producing 52.5 million doses in September 2021, compared with just 8.4 million in August of the same year.[14]

Malaysia also signed a deal in January 2021 with Sinovac to "fill and finish" the vaccines in Malaysia with Pharmaniaga, a government-linked pharmaceutical company.[15] Pharmaniaga imports the bulk material from Sinovac and performs the fill and finish process at the Pharmaniaga LifeScience plant. This also involves transfer of technology and required testing. Subsequently, Pharmaniaga reported that it had supplied 12 million doses of the vaccine to the National COVID-19 Immunisation Programme (PICK) and with the final batch supplied on 21 July 2021. There are subsequently two media reports of further collaboration with China on vaccine R&D and production, although the partners are not named. Moderna is reportedly moving into vaccine production in Malaysia in 2022.

Vietnamese conglomerate Vingroup has teamed up with a US vaccine maker to begin production of its COVID-19 vaccine in Vietnam early next year. On 2 Aug 2021, it was reported that Vingroup began Phase 1 trials of a vaccine developed by Arcturus

ISSUE: 2022 No. 29
ISSN 2335-6677

Therapeutics Holdings, based in the US city of San Diego.[16] Arcturus has agreed to provide the Vietnamese company with an exclusive license to make its mRNA COVID-19 vaccine candidate -- the same type as those developed by Pfizer and Moderna -- solely for sale and use in the country. Arcturus is preparing to start production in March 2022 with a production facility in Hanoi which is capable of producing 200 million doses annually.[17]

Producing Home-Made Covid-19 Vaccines

The desire to produce home-made vaccines is to achieve self-sufficiency, improve coordination among research and development agencies and enhance national capability in Covid-19 vaccine production. There are four countries in SEA that are actively developing home-made vaccines.

Table 3 shows the home-made vaccines that have advanced to clinical trials. Vietnam's Nanocovax, that is being developed by the Nanogen Pharmaceutical Biology Joint Stock Company in cooperation with Military Medical Academy has progressed to Phase 3 trial. But the debut of the first Vietnamese vaccine has been pushed back to 2022, with health authorities taking extra care to ensure the safety and effectiveness of the vaccines.[18]

The ART-021 vaccine that is being developed in Singapore, and the Merah-Putih vaccine in Indonesia are both at Phase 2 trials. Indonesia is pressing to launch the latter's vaccine in the third quarter of 2022.[19] The Nusantara vaccine is however mired in domestic debates as it is being developed by an American company, Aivita Bio Medical Inc., and its choice of vaccine technology is based on dendritic cells, which are components of blood cells that are a part of the immune system. But there are as yet no dendritic cell-based Covid-19 vaccines that have entered Phase 3 clinical trials in the world, or any that have been approved by any drug regulatory authority.[20]

Thailand's two home-grown vaccines are still in Phase 2 trials, with the Chula-Baiya vaccine being plant-based, while its developer Baiya is the first Thai company to enter the university's CU Innovation Hub, a research centre for start-ups, to develop the technology to manufacture recombinant proteins that can produce medicines and vaccines. Mass production of the vaccine Chula Cov-19 is estimated to be in June-September 2022, while the Chula-Baiya vaccine is also expected to be approved for use in the 3rd or 4th quarter of 2022.[21]

ISSUE: 2022 No. 29
ISSN 2335-6677

Table 3. Vaccine candidates in development in Southeast Asia, as at 26 February 2022

	Candidate	Mechanism	Sponsor	Trial Phase	Institution
1	Nanocovax	Recombinant vaccine (Spike protein)	Nanogen Biopharmacuetical	3	Military Medical Academy, (Vietnam)
2	ART-021	RNA vaccine	Artucus Therapeutics and Duke Medical School	2	Duke-NUS Medical School, Singapore
3	Merah-Putih	Inactivated Vaccine	Indonesia-MoH; Airlangga University; Biotis Pharmaceuticals	2	Dr. Soetomo General Hospital, Indonesia
4	Nusantara*	Dendritic cell vaccine, AV Covid-19	Aivita Bio Medical Inc.	2	National Institute of Health and Development, Ministry of Health, Republic of Indonesia
5	ChulaCov19	mRNA-based vaccine	Chulalongkorn University's Center of Excellence in Vaccine Research and Development	2	Chula Vaccine Research Center (ChulaCRC), Faculty of Tropical Medicine, Mahidol University
6	Chula-Baiya	Protein sub-unit	Baiya Phytopharm Co. Ltd., National Vaccine Institute, Thailand	2	Chula Clinical Research Center; Queen Saovabha Memorial Institute

Source: https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker, * https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

ISSUE: 2022 No. 29
ISSN 2335-6677

In January 2022, it was announced that two types of Covid-19 vaccines are being developed in Malaysia. The Institute of Medical Research (IMR), a biomedical research arm of the Ministry of Health, Universiti Putra Malaysia, and the Veterinary Research Institute are collaborating for the development of the first vaccine.[22] This is an inactivated vaccine similar to the Sinovac-CoronaVac vaccine. The second is an mRNA (messenger RNA) vaccine, which is solely an IMR initiative for now. The latter is scheduled for clinical trials in 2024.

CHALLENGES GOING FORWARD

Competing New Vaccines

Home-made vaccines have to struggle to meet stringent regulatory requirements, as well as viable economies of scale for commercial production. The active ingredients needed for making the vaccines as well as other materials have to be imported. This means that new vaccine-producing countries are just shifting from importing final goods (or the vaccines itself) to importing intermediate goods.[23]

At the same time, according to WHO's Covid-19 vaccine tracker, as at February 2022, globally, there are a total of 146 Covid-19 vaccines at the clinical development stage. There is therefore stiff competition with existing vaccines as well as next-generation vaccines that are being developed globally in other countries. In particular, Corbevax, a protein subunit that is being developed by Texas Children's Hospital for Vaccine Development and Baylor College of Medicine in Houston, Texas and Dynavax technologies, is aimed at improving vaccine equity since it carries no patents and uses old recombinant technology for manufacture.[24] Other drug makers are free to use its formulation to reproduce the vaccine, without any payment or complex licensing arrangements. Corbevax is therefore much cheaper and more stable than mRNA vaccines, making it easier to manufacture and distribute on a large scale in developing nations. India has already granted approval for use on people who are above 12 years old and plans to co-produce with the vaccine developers for internal use as well as in the Quad countries.

Trust in Home-made Vaccines

ISEAS's "The State of Southeast Asia's 2022 Survey Report" indicates that trust in home-made vaccines is rather low.[25] The most trusted vaccine brands among Southeast Asians – selected by 54.8% of all respondents – are mRNA vaccines Pfizer and Moderna. Domestic vaccine brands are the second lowest to be trusted, at 0.9 %, which is only slightly higher than the Russian-made vaccine, Sputnik-V.

This implies that even if home-made brands are accepted by national regulatory authorities for emergency use in their own countries, they may not be popular and citizens may still

prefer to use other established brands, unless these are prohibited from being imported or they are priced too high and made unaffordable, through some kind of domestic taxes imposed on imported drugs. The latter policy options even if enforced are highly distortionary and will lead to inefficient resource allocations in the vaccine-producing country. The lack of trust will also stand in the way of exports. Even if these new vaccine-producing countries are to temporarily waive their intellectual property rights to allow less developed countries to produce these vaccines for their own use, as attempted at the WTO level by India and other supporters, demand may again be limited by the lack of trust.

End of the Covid-19 Pandemic and the Need for Booster Shots

At time of writing, the most optimistic scenario is that the end of the current Omicron wave may lead to an end of the pandemic, with natural immunity emerging for a larger share of the population due to the higher numbers infected by this wave. The optimistic scenario renders the manufacturing of new vaccines redundant in the new vaccine-developing countries, unless it is for export to the low-income countries that still need vaccinations to achieve the WHO targets.

The less optimistic scenario is the emergence of new variants, after Omicron. Whether this will lead to a need for more doses of vaccination remains uncertain as there are also recent discussions that three doses of a Covid vaccine — or even just two — are enough to protect most people from serious illness and death for a long time, with diminishing returns on the number of additional doses.[26] Even if additional doses of vaccinations are required, will the newly developed vaccines in SEA be able to provide protection from these new variants? This remains an open question.

CONCLUSION

The race to produce Covid-19 vaccines in SEA is triggered by a general reluctance to be dependent on the vagaries of global supply, imports and donations, and uncertainty over the duration of the pandemic. Joining the exclusive vaccine production club will require SEA countries to enter the vaccine value chain of one of the key producers as a contract manufacturer. While Indonesia and Malaysia have established partnerships with Sinovac, Thailand has teamed up with Astrazeneca, with more partnerships in the offing.

Some SEA countries are also venturing into the production of home-made vaccines. Notably Indonesia, Singapore, Thailand and Vietnam have potential vaccines that have advanced to clinical trials, and they plan to roll out these vaccines in 2022. But, there are numerous other vaccines that are being developed around the world that are also undergoing clinical trials. In particular, Cobervax is touted to be a better candidate for vaccine equity because it carries

ISSUE: 2022 No. 29
ISSN 2335-6677

no patents, relies on long-established recombinant technology for manufacture and has the support of the US and Indian governments.

It remains to be seen whether SEA's home-made vaccines can compete with the new vaccines that are also coming on board as well as the established vaccines, especially when trust in home-made vaccines in SEA is low. It also remains an open question whether future developments in the pandemic may render vaccination and the use of home-made vaccines in SEA redundant or if the new vaccines can combat new variants effectively, given the efficacy record of current vaccines against new variants. Whichever the case, the technology acquired in the vaccine development process can be used to prepare these SEA countries for future pandemics.

ENDNOTES

[1] See https://ourworldindata.org/covid-vaccinations, as at 26 February 2022.
[2] See https://www.who.int/campaigns/vaccine-equity
[3] https://www.reuters.com/business/healthcare-pharmaceuticals/year-after-covid-vaccine-waiver-proposal-wto-talks-are-deadlocked-2021-10-04/
[4] https://www.oxfam.org/en/press-releases/vaccine-monopolies-make-cost-vaccinating-world-against-covid-least-5-times-more
[5] https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30346-2/fulltext
[6] Chad P. Bown and Thomas J. Bollyky, 2021. "How COVID-19 vaccine supply chains emerged in the midst of a pandemic", Peterson Institute of International Economics, Working Paper 21-12, August. https://www.piie.com/sites/default/files/documents/wp21-12.pdf
[7] https://asean.org/wp-content/uploads/2021/10/Agd-6.3.a.i_AVBS_Final_23082019.pdf
[8] https://asean.org/wp-content/uploads/2021/10/Agd-6.3.a.i_AVBS_Final_23082019.pdf
[9] https://www.scmp.com/news/china/science/article/3116707/mass-sinovac-vaccination-programme-set-begin-indonesia-followed
[10] https://www.lexology.com/library/detail.aspx?g=b1b1e2ac-a0cf-4f8f-9a3a-8e212ba05279
[11] Somkid Puttasari 2021. "The failure of vaccine policy pushed Thailand from the best recovering country to the worst." Observer Research Foundation (ORF), 19 August 2021. https://www.orfonline.org/expert-speak/failure-of-vaccine-policy-pushed-thailand/
[12] https://www.ft.com/content/aaa8b820-68c7-408d-9486-222fe2d65634
[13] https://www.voanews.com/a/covid-19-pandemic_thailand-considers-cap-vaccine-exports-covid-cases-surge/6208775.html.
[14] https://globalcommissionforpostpandemicpolicy.org/covid-19-vaccine-production-to-september-30th-2021/
[15] http://www.insage.com.my/Upload/MediaNews/PHARMA/PHARMA-TheSunDaily-13012021.pdf
[16] https://www.biopharma-reporter.com/Article/2021/08/02/Arcturus-Therapeutics-lines-up-clinical-trials-for-next-generation-mRNA-vaccine

[17] https://newsdirect.com/news/vingroup-collaborates-with-arcturus-therapeutics-to-establish-a-manufacturing-facility-in-vietnam-for-arcturus-mrna-covid-19-vaccine-866699795?category=Healthcare
[18] https://asia.nikkei.com/Spotlight/Coronavirus/COVID-vaccines/Vietnam-s-homemade-vaccines-struggle-to-debut-as-COVID-rages2
[19] Indonesia seeks to launch home-grown Covid-19 vaccine in third quarter | The Star
[20] https://en.tempo.co/read/1441394/questioning-nusantara-vaccine
[21] https://www.newswise.com/coronavirus/chula-expects-the-chulacov19-mrna-vaccine-and-chula-baiya-protein-subunit-vaccine-to-be-ready-in-2022/?article_id=761704
[22] https://www.newswise.com/coronavirus/chula-expects-the-chulacov19-mrna-vaccine-and-chula-baiya-protein-subunit-vaccine-to-be-ready-in-2022/?article_id=761704
[23] https://www.oecd.org/coronavirus/policy-responses/using-trade-to-fight-covid-19-manufacturing-and-distributing-vaccines-dc0d37fc/
[24] Could a patent-free vaccine offer a COVID solution that stands up against Alpha, Delta, Omicron, and future variants? - ABC News
[25] https://www.iseas.edu.sg/articles-commentaries/state-of-southeast-asia-survey/the-state-of-southeast-asia-2022-survey-report/
[26] Got a Covid booster? You probably won't need another for a long time. - TODAY (todayonline.com)

ISEAS Perspective is published electronically by: **ISEAS - Yusof Ishak Institute** 30 Heng Mui Keng Terrace Singapore 119614 Main Tel: (65) 6778 0955 Main Fax: (65) 6778 1735 Get Involved with ISEAS. Please click here: https://www.iseas.edu.sg/support	ISEAS - Yusof Ishak Institute accepts no responsibility for facts presented and views expressed. Responsibility rests exclusively with the individual author or authors. No part of this publication may be reproduced in any form without permission. © Copyright is held by the author or authors of each article.	Editorial Chairman: Choi Shing Kwok Editorial Advisor: Tan Chin Tiong Managing Editor: Ooi Kee Beng Editors: William Choong, Lee Poh Onn, Lee Sue-Ann, and Ng Kah Meng Comments are welcome and may be sent to the author(s).