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Strengthening Domestic Vaccine Development and Manufacturing in Vietnam as part of Post-COVID-19 Health Security Response in Vietnam

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Content

- 1. Background and Contextualizing Global Health Security in Viet Nam
- 2. National Plans on Domestic Vaccine Manufacturing and Introduction of New Vaccines
- 3. Existing Local Capacity for Vaccine Development and Manufacturing in Viet Nam
- 4. Strategic Framework for the Strengthening of Viet Nam's Vaccine Development and Manufacturing



Content

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Background

- The COVID-19 pandemic served as a wake-up call for many upper-middle-income country (UMIC) and low-andmiddle income country (LMIC) governments
- Early access to COVID-19 vaccines for the UMICs and LMICs was seriously inadequate, in part due to the concentration of the COVID-19 vaccine R&D and manufacturing by vaccine companies in, and significant upfront purchasing of the COVID-19 vaccines by, the high-income countries
- Further compounded by the widespread prevalence of "vaccine nationalism"
- To counter similar threats in the future, global health stakeholders and countries are compelled to localize and/or expand vaccine-manufacturing capacity and capabilities to strengthen pandemic preparedness, improve vaccine supply security, and tackle endemic diseases sustainably.
- Vietnam government recently signed multiple decisions to strengthen domestic vaccine manufacturing, introduce new vaccines and further improve the domestic supply of vaccines.



What is Health Security?

The World Health Organization (WHO) defines health security as: "the proactive and reactive activities required to minimize the vulnerability to acute public health events that endanger the collective health of populations living across geographical regions and international borders". Health security commonly incorporates a wide range of health risks, including emerging diseases, the social determinants of health like poverty, and social and environmental factors.

Contextualizing Health Security in Vietnam and Expanding its Scope to Include Other Priority Vaccinepreventable Diseases

- In addition to a general threat from an unknown pandemic, Vietnam is also considered a hotspot for influenza virus evolution, both for human seasonal influenza strains, as well as the emergence of zoonotic variants with pandemic potential arising from the interaction of humans, livestock, wild animals, and ecosystems.
- The government also aims to enhance self-reliance for broader vaccine supply as per the population needs.
- For this analysis, known and unknown diseases with epidemic or pandemic potential that can be treated with a
 vaccine and select priority vaccine-preventable diseases identified by the Vietnamese government have also been
 included within the larger conceptual framework of post-pandemic health security in Vietnam.





Content

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National Expanded Program on Immunization (EPI) and Sources of Vaccine Supply

- The national EPI was launched in 1985 with 6 traditional vaccines, and by 2022 has expanded to 14 vaccines including tuberculosis (BCG); polio (IPV and bOPV); diphtheria, pertussis, tetanus, hepatitis B and Haemophilus Influenzae Type b (pentavalent vaccine), Hep B (birth dose), measles and rubella (MR), Japanese B encephalitis (JE), cholera and typhoid (n high-risk areas), and tetanus toxoid (pregnant women).
- The national EPI program provides vaccines against 11 diseases nationwide with some other vaccines available in highrisk areas or for high-risk populations only. Rota, PCV, HPV and Seasonal Influenza vaccines are currently not provided by the national EPI.
- The domestic manufacturers provide all but two vaccines, namely the pentavalent vaccine and IPV, to the national EPI





Key Political Declarations on Domestic Vaccine Manufacturing and Introduction of New Vaccines

- Decision 68/QD-TTg (2014): National strategy for the development of Vietnam's pharmaceutical sector to 2020, vision to 2030: By the year 2020 domestically produced vaccines to meet 100% of the demand for EPI and 30% of the demand for fee-for-service vaccinations.
- Resolution 20 of the Party Central Committee (2017) on strengthening the protection, care and improvement of people's health "Improving research and production capacity of drugs and vaccines: Invest sufficient resources to capture know-how of the production technology of new generation vaccines, polyvalent vaccines, basically meeting the needs of NEPI in the country and towards to exporting vaccine";
 - Decision 1286/QD-TTg (2022) on approving the program to ensure vaccine supply for vaccination until 2030. The decision sets the target to domestically produce a pentavalent vaccine (one of the two vaccines imported by national EPI) by 2025, master the production technology for 15 vaccines, and be able to produce 5 vaccines at international standards by 2030.

- New Vaccines Introduction
- Resolution No. 104/NQ-CP (2022), signed by the Prime Minister, approves the Roadmap to increase the number of vaccines in the EPI for the 2021-2030 period:
- Implementation: Introducing Rota from 2022 (delayed), PCV and HPV vaccines from 2025 and 2026, and seasonal flu vaccines from 2030, respectively. The vaccines will be scaled up in a phased manner.
- Funding sources: The state budget shall provide funding for the purchase of vaccines under the roadmap and the local government budget shall provide funding for the organization of local immunization.



Concrete Actions and Progress

 Domestic Vaccines Manufacturing: No clarity on concrete actions taken or plans to materialize the political declarations on the strengthening of vaccine manufacturing in the country

New Vaccines Introduction:

- Rota and Seasonal Influenza Vaccines are domestically produced; PCV and HPV vaccines are currently not in the portfolio or plans of any domestic manufacturer
- Rota vaccine (planned for 2022 introduction) is in the process of being introduced in the country with support from Gavi (middle-income country approach)
 - Gavi-supported Rota vaccine is initially being imported but later it is expected that the government will use the domestically produced Rota vaccine in Viet Nam
- GDPM and Unicef have prepared the budget estimates^A for the procurement of these four vaccines

Vaccines		2023	2024		2025		2026		2027		2028		2029		2030	2040
Rota	\$	956,926	\$ 7,075,621	\$	7,148,828	\$	7,222,787	\$	7,296,747	\$	7,371,465	\$	7,446,951	\$	7,523,209	\$ 8,330,092
Provinces	s		63	63	5	6	3	6	53	(63	6	3	6	53	63
PCV (Unicef Lowest Price)	\$	-	\$-	\$	393,027	\$	847,456	\$	1,259,320	\$	1,483,869	\$	1,691,612	\$	1,928,918	\$ 4,050,727
PCV (Unicef Highest Price)	\$	-	\$-	\$	648,495	\$	1,398,302	\$	2,077,878	\$	2,448,384	\$	2,791,160	\$	3,121,786	\$ 6,555,751
Provinces	s				Ę	5	10)	1	5	20)	25	5	30	63
HPV (Unicef Lowest Price)	\$	-	\$-	\$	-	\$	131,228	\$	168,652	\$	200,010	\$	223,634	\$	252,900	\$ 1,991,590
HPV (Unicef Highest Price)	\$	-	\$-	\$	-	\$	203,630	\$	261,702	\$	310,361	\$	347,018	\$	392,432	\$ 3,090,398
Provinces	s						4	1		5	6	5	7	7	8	63
Seasonal Influenza	\$	-	\$-	\$	-	\$	-	\$	-	\$	-	\$	-	\$	11,050,499	\$ 34,809,071
Provinces	s														8	63







Content

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Domestic Manufacturers: Supply

- Strong history of domestic vaccine production by four state-owned vaccine manufacturers IVAC, POLYVAC, VABIOTECH, and DAVAC.
- The total annual production capacity (F&F) of these four manufacturers for 13 different vaccines is 40 million doses whereas the annual consumption (supply volume) of these vaccines across the public and private sectors is approximately 32 million doses a year (2023)
- ~81% of these vaccines by volume are for the national EPI and the rest are used in the private sector (including fee-for-service at public health facilities)





Domestic Manufacturers: Manufacturing Capabilities, Estimated Production Capacity and R&D Portfolio of Vaccines (2023)

						Annual Damand in		
Manufacturer	Vaccine	Platform Technology	Currently Produced (API + F&F)	API* Only	F&F Only	Annual Capacity of API + F&F Production (million doses)	In R&D	Annual Demand In Vietnam (in million doses)
	1. Hepatitis B	Subunit	\checkmark	Х	Х	20		2-2.5 (EPI + Private)
	2. Hepatitis A	Inactivated	\checkmark	Х	Х	0.3		0.35-0.40 (EPI + Private)
Vabiotech	3. JE (mouse brain)	Inactivated	\checkmark	Х	Х	6		5.5
Vabiolecii	4. Oral Cholera	Killed whole cell	\checkmark	Х	Х	8		0.5 (Private)
	5.JE (cell-based)	Inactivated					\checkmark	2 (EPI) + 2 (Private)
	6.Hib conjugate	Subunit		\checkmark	6-9 (EPI + Private)			
	1. DTP* (includes Td vaccine capacity)	Inactivated	\checkmark	Х	Х	6		3-4 (EPI)
	2. TT	Toxoid	\checkmark	Х	Х	10		6-9 (EPI + Private)
IVAC	3. BCG	Inactivated	\checkmark	Х	Х	2-3		2-4 (EPI + Private)
	4. Seasonal Flu	Inactivated	\checkmark	Х	Х	0.3		2-3 (EPI + Private)
	1. Pandemic Flu	Inactivated					<	
	1. OPV	Live-attenuated	✓	Х	Х	10		6 (EPI)
	2. Measles	Live-attenuated	✓	Х	Х	3		2-3 (EPI)
POLYVAC	3. Measles and Rubella	Live-attenuated	~	Х	х	3		2-3 (EPI)
	4. Rota	Live-attenuated	\checkmark	Х	Х	0.2-0.3		20 (EPI)
DAVAC	1. Typhoid fever Vi polysaccharide	Subunit	~	Х	х	3-5		0.3 (Private)

Despite producing adequate supply for the national EPI and private sector, none of the vaccine manufacturers in Vietnam have reached maximum production capacity due to: (1) export limitations, as most vaccines have not been pre-qualified by WHO, and (2) preference to purchase imported vaccines among higher-income populations.

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Current Capacity among Vietnamese Manufacturers for Different Vaccines and Value Chain Steps

- Established in the space of monovalent vaccines, with limited presence in new (second-generation) and pandemic vaccines
- No in-country capacity for pre-clinical research

R&D

Production

		Legacy / Routine								Ex	New / pandi	ng	Endemic			Novel						
	BCG	DTP	Pentavalent	Hexavalent	Hepatitis A	Hepatitis B	Measles/MR	Tetanus	Typhoid	Polio (bOPV)	НРV	Rota	PCV	Japanese Encephalitis	Seasonal Inlfuenza	Cholera	Meningococcal	Covid-19	ЫV	RSV	TB	Malaria
Pre-Clinical														۲								
Clinical Ph1																						
Clinical Ph2																						
Clinical Ph3																						
API	•					•	•		•			•		•		•						
F&F														•								

Number of manufacturers

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Current Capacity among Vietnamese Manufacturers by Vaccine Platforms

 Strongly rooted in traditional vaccine platform technologies with limited capacity in selected modern and novel vaccine platforms

	Traditional	/ Classical	Мо	dern	Novel / Next Generation						
	Live- Attenuated	Killed or Inactivated	Toxoid	Sub-unit	Nucleic acid (mRNA)	Viral Vector	Virus-like Particles	Antigen- presenting Cells			
Vabiotech	•	•		•		•					
IVAC						•	•				
POLYVAC		•			•						
DAVAC				•							
Nanogen				•							
VinBioCare*					•						



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Content

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Strategic framework for strengthening Vietnam's vaccine development and manufacturing industry

- Output: Instant and supply strategic prioritization of the existing portfolio based on manufacturing complexity, demand and supply constraints
- 2 Capabilities required in the context of a threat of a pandemic
- 3 Market access for reduced business risk
- 4 Collaboration for **technology transfer** and product development
- 5 Local enabling ecosystem in Vietnam to support the domestic vaccine industry national regulatory authority (NRA) strengthening, talent pool upgrading, commitment from the government on the purchasing of vaccines from local manufacturers



O Strategic prioritization based on manufacturing complexity, demand and supply constraints

FEASIBILITY

VABIOTECH

- The aim for domestic manufacturers must be to approach self-sufficiency in end-to-end vaccine production in long-term, so the suitability of the targeted portfolio, from pathogen type to valency (monovalent or multivalent) to technology platforms while considering the existing portfolio and capabilities, is important
- Briefly, there are two ways to group vaccines based on the complexity
 - Valency: Monovalent (Hep A, Hep B, Rota; less complex to develop/produce) v Multivalent (pentavalent, hexavalent; more complex and command a higher price/profit)
 - Technology: Traditional platforms have relatively lower production complexity in general compared to modern (subunit, recombinant) and novel platforms (mRNA) which tend to generate more profits



Strategic prioritization based on manufacturing complexity, demand and supply constraints (contd.)

DEMAND

- Low volume sales would struggle to turn itself economically viable
- While a huge domestic market backs Indian and Chinese manufacturers, Vietnamese manufacturers must serve beyond Vietnam to achieve economies of scale. The ASEAN region potentially represents a sizable market demand for larger volume facilities.

Estimated Demand (Million Doses) of Different Antigens in the ASEAN Region in the Period 2023-2030







DEMAND

O Strategic prioritization based on manufacturing complexity, demand and supply constraints (contd.)

SUPPLY

- For many vaccines, the market is already saturated, and prices are extremely low. The efforts should rather concentrate on supplyconstrained vaccines for the time being.
 - For instance, BCG and pentavalent vaccines might appear attractive owing to their large market size, but the markets are characterized by fierce competition, with no supply shortage and dose prices averaging in cents
 - Far more promising would be products like OCV, which still suffer supply shortages (despite having a smaller market) and which have relatively low manufacturing complexity. A similar case can be made for Rota, Measles and Measles-Rubella vaccines.

Volume Purchased and Supply Base of Relevant Vaccines (2021)



one hexavalent vaccine manufacturer is in process to receive WHO prequalification by end of 2023 * one manufacturer will exit the market at the end of 2023

**** a second malaria vaccine is currently in process of receiving WHO prequalification



O Strategic prioritization based on manufacturing complexity, demand and supply constraints (contd.)

- Given that Vietnam's domestic companies are mostly concentrated in the production of monovalent vaccines, the potential of the
 existing monovalent vaccines for overseas business should be assessed in short-term while the capabilities to produce other new
 vaccines (mono or multivalent vaccines) on modern or novel platforms are developed in the medium-to-long term.
- For indicative analysis: the potential vaccine candidates in the short term from the current product portfolio of Vietnamese manufacturers are OCV, Measles-Rubella and Measles, and Rota vaccines. Vabiotech has OCV in its portfolio whereas the other three vaccines are included in the product portfolio of POLYVAC.



Supply constraints (no. of existing global suppliers, supply meets demand, country preferences, buffer capacity)

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2 Capabilities required in the context of a threat of a pandemic

- The risk of a pandemic from a seasonal influenza strain is highly relevant for Vietnam in addition to the general threat of an unknown pandemic
- However the current level of seasonal influenza vaccine production capacity in the country is approximately 0.3 million doses annually. There haven't been any long-term plans under the government aimed at industrial preparedness for an influenza pandemic through improved R&D and manufacturing.
- The decision to introduce the seasonal influenza vaccine as part of the national EPI starting from 2030 was only taken last year
- Having expanded capacity for yearly seasonal influenza vaccine production in place will help ensure that manufacturers are available to quickly switch to pandemic vaccine production if such a need arises.
- The current technological capabilities in terms of vaccine platforms do not allow for rapid initiation of studies and manufacturing at scale in the event of an pandemic

Capabilities required in the context of a threat of a pandemic (contd.)

- Safeguarding against the event of a pandemic requires targeting manufacturing platforms that have a proven ability to rapidly scale up the production of pandemic-appropriate vaccines
- mRNA offers the best potential to enable almost immediate initiation of human studies in the event of an outbreak of an unknown pathogen followed by viral vector and recombinant protein platforms. Therefore, to manage the risk of a future pandemic in Vietnam, Vietnamese manufacturers will need to invest in these novel vaccine platforms.

			Timeline suitable for	r 100 day goal Po	otential to reach 100 days (with	targeted preparation
Platform	Description	Minimal time until first batch ¹	Ability to pre-optimise processes prior to outbreak	CD independent of immunogen knowledge	Key limitations	Example vaccines
RNA	Delivery of RNA of antigen using lipid nanoparticles (LNPs)	3+ weeks	Similar process (assuming use of same LNP)		Plasmid DNA can be rate- limiting raw material	COVID-19
Viral vector	Delivery of DNA or RNA of antigen using viral vectors	10-12 weeks	Unique viral banks required	\otimes	Long release assays required (e.g., replication competent virus)	COVID-19, Ebola, Zika, influenza, HIV
Recombinant protein	Protein vaccine based on viral antigens	Similar to viral vector	Optimise cell growth, protein folding & formulation w/ adjuvant	Viral antigen needs to be known & targetable	Protein folding and formulation difficult to standardise	COVID-19, hepatitis B, shingles HPV
Virus-like Particles	Virus-resembling molecules with multiple surface antigens	Longer than recombinant proteins	 Optimise cell growth, protein folding, complex assembly and formulation 		Protein folding and formulation difficult to standardise; complex molecules due to need for self-assembly	Hepatitis B, HPV
Inactivated vaccine	Inactivated or altered replication-deficient virus	Speed determined by ability to use high	Relatively simple to manufacture but growth may be virus-specific	Whole virus vaccines	Ö Weaker immune response multiple doses; release test to ensure full inactivation	COVID-19, influenza (shot), hepatitis A, polio (shot), rabies
Live attenuated vaccine	Genetically modified virus which does not cause disease	line availability & scalability and viral doubling time	Genetic manipulation unique to virus	requires limited knowledge of specific antigens	Not suitable for people with compromised immune system	MMR, rotavirus, smallpox, shingles, yellow fever

Suitability of Vaccine Platforms for Rapid Response

Timelines until first batch vary between platforms but so does their immune response & side effect profile and need for immunogen identification



3 Market access for reduced business risk

- Confirmed access to the market is a basic requirement to achieve a sustainable vaccine manufacturing footprint. Procurement commitments directly from other country governments or indirectly via global vaccine procurement coordinators have been crucial in supporting the growth of the vaccine industry in India, China and other countries (Indonesia, Brazil).
- It would therefore be critical for Vietnamese manufacturers to explore such pull mechanisms (via Gavi, Unicef or another agency) for the strategically identified vaccines from their current portfolio, for global expansion.
- In the ASEAN region, many countries have or are phasing out of vaccine procurement support provided by Gavi. Therefore, the direct commitments of ASEAN governments to procure regionally will be critical. In the absence of such commitments, a new and innovative regional mechanism might be required. One such recent regional initiative has been the Asia Pacific Vaccine Access Facility (APVAX), focused on COVID-19 vaccine procurement, established by ADB.
- In addition to the pull mechanisms discussed above, there are other push mechanisms that can be explored



Collaboration for technology transfer and product development

- Vietnamese manufacturers hold substantial experience in technology transfer or product development (see table)
- However, no sustainable R&D capacity has been developed or product collaboration/technology transfer agreements have been signed to embark on a sustainable shift to modern or novel technology platforms
- For modern platform antigens such as HPV and PCV vaccines that are not domestically manufactured but are expected to be introduced and scaled up in Vietnam over the coming decade, it is critical to facilitate technology transfer partnerships if the country wants to continue being self-reliant for its vaccine procurement. These vaccines also present a viable business opportunity in the ASEAN region.
- In the case of pandemic threats, such partnerships need to be formed for the novel vaccine platforms (e.g. mRNA and viral vectors)

Vaccine	Technology Platform	Vietnam Manufacturer	Technology Partner	Value Step Chain	Rolled Out by EPI
Нер В	Subunit	Vabiotech	Green Cross (S. Korea)	API + F&F	Yes
Typhoid Vi Polysaccharide	Subunit	DAVAC	NIH (USA)	API + F&F	No
Seasonal Influenza	Inactivated	IVAC	WHO and PATH	API + F&F	No
Measles	Live-attenuated	POLYVAC	Kitasato Institute (Japan)	API + F&F	Yes
Measles-Rubella	Live-attenuated	POLYVAC	Daiichi Sankyo Biotech (Japan)	API + F&F	No
Covid-19*	mRNA	VinBioCare	Arcturus Therapeutics (US)	F&F	No





6 Local enabling ecosystem in Vietnam for the support of the vaccine industry

Environment	Short-term	Clarity and Commitment from the Vietnam Government on Purchasing	 Vaccines are purchased on the annual basis however there is no assurance or clarity around procurement mechanisms; uncertainty prevails at the level of manufacturers if and when their vaccines will be procured by the government Prices of domestic vaccines are set by the Ministry of Finance, though they have not been adjusted since 2008 It critical that the government signals the local demand strongly and potentially in the long-term that could act as an incentive to invest in the capabilities for future vaccines. Longer-term purchase agreements could also be instrumental in attracting global partners and incentivizing partnerships.
Local Enabling	Medium-term	Vietnam National Regulatory Authority (NRA) Strengthening	 None of the vaccines produced domestically in Vietnam currently have WHO PQ approval which bears a significant impact on the local manufacturers' ability to export their products internationally. Vietnam NRA are certified Level 3 by WHO but they are still short of the resources and capacity needed to support or expedite the WHO PQ processes and certification of new technology vaccines
	Long-term	Talent Upskilling of Workforce	 Inculcate practical learning experience through secondments with experienced manufacturers and R&D organizations and bringing global experts to work at local manufacturing sites in Vietnam Capacity building should be emphasized as part of technology transfers and gaps should be identified and filled in tertiary and vocational education courses relevant for vaccine manufacturing.

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Strategic Directions for the Strengthening of Vietnam Vaccine **Manufacturing**



Increasing manufacturing Complexity