Delay in Vaccine Access in Asia-Pacific countries

Nilubon Subsittipong

The Graduate School

Yonsei University

Department of Pharmaceutical Medicine and Regulatory Sciences

Delay in Vaccine Access in Asia-Pacific countries

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Nilubon Subsittipong

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This certifies that the master thesis
of Nilubon Subsittipong is approved.

_____
Thesis Supervisor: [Euna Han]

_____
[Taehyun Kim: Thesis Committee Member #1]

_____
[Junjeong Choi: Thesis Committee Member #2]

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Abstract

Background: The introduction of new vaccines has been delayed in some Asia-Pacific countries and lead to delay in vaccine access for target patients. However, the approval lag of vaccine in Asia-Pacific countriess has not been assessed. This study aimed to evaluate the availability and approval lag of vaccines in Asia-Pacific countries and compare with the United States (US), and European Union (EU).

Methods: The information of vaccines prequalified by the World Health Organization (WHO) between 2010 and 2019 was obtained primarily from WHO website. The date of approval of WHO prequalified vaccines in Australia, India, South Korea, Thailand, Singapore, Malaysia, US and EU were retrieved from the official website of national regulatory agencies. The vaccines were divided into 2 groups based on their first approval pathway, i.e., vaccines that first approved by SRA and those that first by non-SRA. Absolute approval lag was the availability of vaccines. Relative approval lag was calculated from the lag time between the approval date in certain country and the first global approval date as median approval lag. Man-Whitney U Test was used to assess statistical differences between relative approval lag between SRA first and non-SRA first group.

Results: Total of 92 vaccines were prequalified by WHO between 2010 and 2019, but only 61 vaccines were included in the analysis. Over 50% of vaccines were first licensed by Non-SRAs. Of all WHO-prequalified vaccine, the median approval lag in Asia Pacific countries was longer than those in the US and EU, with 30 months in Australia, 15 months in South Korea, 52 months in Thailand, and 23 months in Singapore compared to 0 months

in the US and EU. The differences in approval lag between SRA first vaccines and Non-SRA first vaccines were statistically significant in South Korea and India ($P < 0.05$).

Conclusions: The approval lag of vaccines was observed in the Asia-pacific countries, indicating a gap between Asia-Pacific countries, the US, and EU in regard to access to new vaccines. Future studies need to analyze the background factors related to the gap in the availability and vaccine approval lag in Asia-Pacific countries and assess the impact of vaccine approval lag in the region.

I. Introduction

Population living the Asia-Pacific region accounts for nearly two-thirds of the world's population.The region has high diversity in cultural, political, economic diversity and other areas that influence vaccine development, implementation, and registration such as.(1) In a decade, Asia has transformed from low to middle-income region to lower-middle incomes to high-income region. (2) However, the transformation was not equal across countries. High-income and low-middle income countries still have different vaccine development, implementation, and registration process.

The differences in vaccine development in the region include all steps of vaccine innovation, production, and consumption. The region includes China, India, Indonesia, and Vietnam, which are eligible countries or graduate countries from The Global Alliance for Vaccines and Immunization (Gavi). They have manufacturers of vaccines in their countries. The region also includes Korea, which is the country in the 12 Developing Country Vaccine Manufacturers Network (DCVMN) that produce over 50% of United Nations (UN) agency-procured vaccines doses. In the Asia-Pacific region, vaccine manufacturers have transformed from downstream vaccine processing providers to innovators of more affordable previously approved vaccines and innovators of novel vaccines.(1) Financial funding in biomedical research and development (R&D) in Asia-Pacific region has increased to 23.8% of the global share, while decreased in the United States (US), Canada, and Europe. (3). The trend could be due to the pharmaceutical industry recognition of highly growth vaccine opportunities in Asia.(1)

Asia-Pacific region has a problem in the vaccine access. The region do not have a central regulatory approval process like European Medicines Agency (EMA) in Europe or the Pan American Health Organization (PAHO), which coordinates regional immunization program and centrally purchases eligible vaccines.(1) The diversity in regulatory requirements and procedures delay the vaccine's marketing authorization, and consequently leads to a delay in access to safe and effective vaccines that may prevent significant morbidity and mortality in their populations(4)

There were several efforts to streamline regulatory requirements between countries and regions. There also were efforts to encourage mutual recognition practices between national regulatory authorities to preserve resources and time and avoid redundancy in Asia.(4) For example, the Association of Southeast Asian Nations (ASEAN) introduced the sub-regional regulatory harmonization to improve in technical requirements and regulatory procedures. It aimed to ease marketing and technical differences.(1) However, local regulatory agencies adjust Common Technical Dossier (CTD) template, defeating the original objective of harmonization. Consequently, the differences in requirements are still high, particularly in structure numbering and contents and the registration processes.(4) This would restrict vaccine access for people in the region due to the increase in preparatory dossiers related to the same product to fulfill with the specific requirements for certain countries and the different timeline of each national regulatory agency for evaluation of the submitted information.(2)

Drug lag or approval lag refers to a delay in availability in the country, calculated from the different approval date between an approval date in a certain country and world first approval date. Drug development and registration in Asia are commonly delayed behind the US and EU, leading to a crucial unmet need due to restricted or delayed drug for Asian populations.(5) There are numerous factors related to approval lag, including molecular type, therapeutic class, status of orphan drug, registration and review procedure, nationality, the requirement for local data, and the global clinical trials.(6) Previous studies have examined drug approval duration and drug lag in some countries. For example, Lee et al (6) compared drug lag in Korea and Japan between 2009 to 2017 and its relevant influencing factors. The results showed the shorter drug lag in Korea than in Japan.

The associated factor with median lag time in Korea was domestic company. The factor associated with median lag time in Japan was orphan drug status. The authors suggest that the shorter drug lag in Korea could be explained by the existing past knowledge in new pharmaceutical development. The global clinical trials conducted in Korea is higher than in Japan. Inclusion in global clinical trials is important in clinical development strategy to decrease drug lag. Kataria et al (7) compared the approval lag for new drugs of cardiovascular diseases between India and the US and EU, and confirmed approval lag in new cardiovascular drugs in India.

Objective of study

There is no comparison study in the approval lag of vaccine in Asia Pacific regions. The objective of this study was to evaluate the availability and approval lag of vaccines in Asia-Pacific countries and compare among Asia-Pacific countries, the US, and EU.

Significance of study

The comparison study on approval lag will allow us to understand the gaps in availability and delay in access to vaccines in different countries in the Asia-Pacific region. The information can be used to support for improvement of vaccine access in the region.

II. Literature reviews

2.1 The importance of vaccines

Vaccine is a highly cost-effective intervention to prevent infectious diseases with rarely serious adverse reactions. (8) The effective vaccination has made a great contribution to children, families, communities, economies, and global health. The vaccination not only protects people from vaccine preventable diseases which are the causes of millions of deaths per year, but also saves time and money to their families and reduces the social and economic burden of the disease on communities. (9,10)

2.2 Vaccine preventable disease

Vaccine-preventable disease (VPD) is the bacterial and viral disease that can be avoided with vaccines. VPDs can spread through the air, respiratory droplets, and bodily touch and other methods. Measles, for example, is a highly infectious disease with two hours after a person with measles has left the room. Due to the implementation of immunization with effective vaccines, many of VPDs have significantly decreased. However, the VPD awareness remains a top priority so that the public and healthcare practitioners should understand the importance of VPD to keep an eye on vaccination against those diseases. (11) The major vaccine-preventable diseases provided by WHO are shown in Table 1. Most of VPDs are covered by vaccines in the National Immunization Program, depending on the incidence of the certain in each country.(12)

Table 1 the major vaccine-preventable diseases and the associated vaccines (12)

Pathogens	**Vaccines**
Tubercle bacillus	Bacillus Calmette-Guérin (BCG) vaccine
Poliovirus	Oral polio vaccine (OPV) vaccine, Inactivated polio vaccine (IPV) vaccine
Corynebacterium diphtheriae (Diphtheria)	Diphtheria toxoid vaccine
Clostridium tetani (Tetanus)	Tetanus toxoid (TT) vaccine
Pertussis	Whole-cell pertussis (wP) vaccine, Acellular (cell-free) pertussis (aP) vaccine
Measles virus	Measles vaccine
Hepatitis B virus	Hepatitis B vaccine
Rotavirus	Rotavirus vaccine
Haemophilus influenzae type B (Hib)	Hib conjugate vaccine
Streptococcus Pneumoniae (Pneumococcal infection)	Pneumococcal vaccines
Yellow fever virus	Yellow fever vaccine

The brief summary of each vaccine preventable disease.

1. Cholera

WHO recommends Cholera vaccine in the endemic region during cholera outbreaks. Cholera is an acute bacterial disease that causes diarrhea. Cholera has been estimated to cause around 1.3 to 4.0 million cases per year with 21,000 to 143,

000 death. The 99% of cholera cases occurs in Africa and southern Asia. Cholera can cause endemic and epidemic.(13,14)

2. Ebola

In 2019, the Ebola virus vaccine was firstly approved in the US to protect EVD. However, it had been used in 2018-2020 to prevent Ebola in more than 350,000 people in Guinea. Ebola virus disease (EVD) is uncommon but very severe hemorrhagic fever with 50% of an average case-fatality rate and varies from 25% to 90% during the outbreak. In 2014-2015, the largest Ebola outbreak occurred in West Africa. It started from Guinea and spread to Sierra Leone and Liberia.(15) EVD had also been imported to the US through nine of EVD cases from an epidermic region and transmitted to two US healthcare workers while taking care of the first EVD case in the U.S.(16) The importation of the EVD case also occurred in the UK, Spain and Italy.(15)

3. *Haemophilus influenzae* type b

Haemophilus influenzae type b (Hib) causes serios bacterial infections, such as pneumonia, meningitis, mainly in children aged under 5 years. The disease burden was high in low-income countries. WHO recommends Hib conjugate vaccine for prevention of Hib disease in the national immunization program. (17)

4. Hepatitis A

Hepatitis A is a liver disease caused by hepatitis A virus (HAV). The symptoms range from mild to severe illness. WHO reported an estimated 7,000

deaths from hepatitis A in 2016 with 0.5% mortality rate. The hepatitis A vaccine is recommended for the people who are at high risk. (18)

5. Human Papillomavirus

Human Papillomavirus (HPV) is the cause of viral reproductive tract infection. Among HPV types, more than 14 types are high risk types that can cause cancer, with 70% of cervical cancer HPV type 16 and 18. HPV is also associated with anal cancer, vulvar, vaginal cancer, penile cancer, and oropharyngeal cancer. WHO recommends HPB type 16 and 18 vaccine to prevent cervical cancer. (19)

6. Influenza

Seasonal influenza is an acute viral respiratory infection. Globally, seasonal influenza causes approximately 3 to 5 million severe cases and up to 650,000 respiratory mortality every year. (20,21) Influenza vaccine is an essential key to reduce the health and economic burden of influenza. The timing of getting an influenza vaccine is different from other vaccines. WHO recommends that people should get an influenza vaccine once a year (21). The reasons for getting an influenza vaccine every years are that the influenza viruses are always mutating, the vaccine is need to be up-to-date every year to prevent the viruses that may be the most prevalent for the upcoming flu season (22).

7. Japanese Encephalitis

Japanese encephalitis virus (JEV) is the major cause of viral encephalitis in Asia with approximately 68,000 cases per year with up to 30% of the case-

fatality rate. An estimated 30%-50% of patients has permanent neurologic or psychiatric disorders as consequences of disease. Endemic JEV transmission occurs in 24 countries in South-East Asia and West Pacific areas with over 3 billion people are at risk for JE. WHO recommends the national immunization of JE vaccine in endemic districts.(23)

8. Measles

Measles is a severe and easily transmittable infection caused by viruses in the paramyxovirus family. 140,000 deaths from measles were reported worldwide, particularly in children aged less than 5 years old. Measle containing vaccine is recommended to include in the national immunization of measles vaccine.(24)

9. Meningococcal meningitis

Meningococcal meningitis is a bacterial serious infection, associated with a high fatality rate. Meningococcal meningitis was reported globally, but the disease burden was the highest in sub-Sahara Africa. Vaccine is used to prevent Meningococcal meningitis, particularly in the outbreak.(25)

10. Pneumococcal infection

Pneumococcal infection (PD) is a global major public health with15% of all death of children under 5 year-old (26). There is a high burden of PD in Asia and the highest number of death from PD and high incidence were reported in South Asia. (27) Immunization by pneumococcal conjugated vaccine is an essential way to decrease PD rates.

11. Polio

Polio is a viral infection, which invades the neurological system, mainly reported in children aged less than 5 years old. Irreversible paralysis was reported in 1 in 200 infectious cases with 5%-10% death in paralyzed case. However, the effective vaccine reduced the infection with only 33 reported cases in 2018.(28)

12. Rabies

Rabies is a vaccine preventable zoonotic disease caused by viruses from animal, particularly in dogs. The fatality rate is nearly 100% when symptoms occur. Over ten thousands deaths from rabies were reported, particularly in Asia and Africa.(29)

13. Rotavirus

Rotavirus is the severe diarrheal disease, most commonly in children globally. WHO estimated 215,000 deaths of children aged less than 5 years old from rotavirus infection every year in 2013, particularly in low-income countries. WHO recommends rotavirus vaccines in all national immunization program and give a priority to South and Southeast Asia and sub-Sahara Africa. (30)

14. Tetanus

Tetanus is an acute infection cause by the bacterium *Clostridium tetani* through the cut or wound on the skin. Birth-associated tetanus in infant and mothers were mainly reported in those who have not vaccinated. In 2015, neonatal tetanus caused approximately 34,000 infant deaths. Tetanus-toxoid-containing

vaccines (TTCV) can prevent tetanus. It is also necessary for people, who already infected and recovered from tetanus, to get vaccination because they can be infected again.(31)

15. Typhoid

Typhoid fever is a severe bacterial infectious disease, caused by *Salmonella Typhi*. Approximately 11-20 million cases were reported with 128,000-161,000 deaths per year. There are two vaccines for the prevention of typhoid. WHO prequalified new conjugated vaccines with prolonged immunity in 2017. (32)

16. Varicella

Varicella-zoster virus (VZV) is the cause of varicella by primary infection and Herpes Zoster by reactivation of a virus. The circulation of VZV is worldwide, affecting more than 90% of adolescence if a vaccination program is not available. The disease is an acute and highly transmissible disease. The symptoms are usually mild but the severe and fatal complication, such as cellulitis, pneumonia, encephalitis, can occur. The disease can be prevented by the varicella vaccine that is available as a single or in combination with measles, mumps and rubella vaccine. (33,34)

2.3 New vaccine introduction in the Asia-Pacific region

The introduction of new vaccines in some Asia-Pacific countries has been delayed. There are several contributing factors, that impact the new vaccine introduction, including insufficient local data on the disease burden and vaccine impact on the economy to for the

inclusion of vaccine in national immunization programs, lack of financial resources (35) and differences in vaccine development and registration process (1).

2.4 National immunization programs

A national immunization program (NIP) is a government program to provide immunization services to protect all people from vaccine-preventable disease at no cost. A NIP is interchangeable with the Expanded Program on Immunization (EPI) that was created from purpose to avoiding preventing vaccine-preventable diseases in children.(36)

Key factors for adding a vaccine to NIP include three areas. First, the considering factors, relating to disease that is prevented by the vaccine, include a public health priority, the disease burden in the country, and the status of other disease prevention and control methods. Second, the considering factors relating to the vaccines include the efficacy, safety and other characteristics of available vaccine, economic and financial issues, and availability of vaccine. The last considering factor is the strength of the immunization program and health system.(37)

However, insufficient local data on the disease burden and vaccine impact on the economy to limit the evidence-based decisions to add new vaccines to NIPs in Asia-Pacific region, especially in low-middle income countries. It is difficult to acquire government decision and financial support to the inclusion of vaccines in NIPs without such data.(35)

The NIPs of selected Asia-Pacific countries are summarized in Table 2 and (38–44) All NIPs in these countries had covered diphtheria-tetanus-pertussis (DTP), poliomyelitis, and measles. Human papillomavirus vaccine (HPV) was included in NIP of

all countries except India. The disease burden is one of the important factors for adding the vaccine in NIP. Japanese encephalitis (JE) vaccine was included in NIP of South Korea, Thailand, India, Malaysia due to the prevalence of JE in the countries. Seasonal influenza vaccine only included in NIP of South Korea, while is still alternative in most countries.

Table 2 National immunization program in Asia-Pacific countries.

	Australia	South Korea	India	Singapore	Thailand	Malaysia
Bacillus Calmette-Guérin (BCG)		✓	✓	✓	✓	✓
Hepatitis B virus (HBV)	✓	✓	✓	✓	✓	✓
Diphtheria-tetanus-pertussis (DTP)	✓	✓	✓	✓	✓	✓
Poliomyelitis (Polio)	✓	✓	✓	✓	✓	✓
Haemophilus influenzae, type B (Hib)	✓		✓	✓		✓
Measle	✓	✓	✓	✓	✓	✓
Varicella	✓	✓		✓		
Japanese encephalitis (JE)		✓	✓[b]		✓	✓[a]
Rotavirus	✓		✓			
pneumococcal conjugated vaccine (PCV)	✓			✓		✓
meningococcal conjugated vaccine (MenCCV)	✓					
Influenza		✓				
hepatitis A vaccine (HAV)	✓	✓				
Human papillomavirus vaccine (HPV)	✓	✓		✓	✓	✓

Note: Adapted from Lu CY, et al. 2012;30(13):2252. (38)
[a] In the state of Sarawak only.
[b] In endemic districts only

Differences in vaccine composition for certain vaccines are summarized in Table 3. (38–44) Whole cell Diphtheria-tetanus-pertussis was only used in NIP of Thailand and India, while other used acellular DTP. Oral poliovirus vaccine (OPV) was used in India,

Singapore, Thailand, while others used inactivated poliovirus vaccine (IPV) or IPV-containing combination vaccines. (38)

Table 3 The list of different vaccine types in national immunization program

	Australia	South Korea	India	Singapore	Thailand	Malaysia
Diphtheria-tetanus-pertussis	Acellular	Acellular	Whole cell	Acellular	Whole cell	Acellular
Poliomyelitis	DTPa-IPV/Hib/HPV	IPV	OPV	OPV	OPV	DTPa-IPV/Hib
Haemophilus influenzae, type B	DTPa-IPV/Hib/HPV	-	DTP/HBV/Hib	Hib	-	DTPa-IPV/Hib
Measles-containing vaccines	MMR	MMR	MR	MMR	MMR	MMR

Note: Adapted from Lu CY, et al. 2012;30(13):2252. (38)

2.5 Vaccine financial resources

The introduction of vaccines was delayed in some Asia-Pacific countries.(35) There are challenges in introducing vaccines into in Asia-Pacific countries due to their economic diversity. The region contains high-income countries where are economically developed countries, middle-income countries where are economically developing countries, low-income countries where do not have very developed economies. (45).

In low-middle income countries, access to new vaccines is delayed than those in high-income countries. There is a global public-private health corporation called the Global Alliance for Vaccines and Immunization (GAVI), which help poor countries get access vaccines with full financial support(46), so low-income countries can get access to vaccine through this external support. While most middle-income countries are not qualified for full financial support from GAVI and facing with high price vaccines and

limited and unpredictable funding in their countries. The lack of financial resources may slow down access to new vaccines in middle-income countries. (9,35)

2.6 WHO prequalification and Vaccine registration

2.6.1 WHO prequalification

WHO prequalification is a systematic process to assess and ensure that pharmaceutical products, complied with global standards of quality, safety and efficacy. It intended to give United Nations (UN) procurement agencies the choice of a range of quality healthcare products and the list of prequalified products has also become a helpful tool for bulk buyers including countries themselves and other organization (47).

The target countries of WHO-prequalified products are lower- middle income and low-income countries. Therefore, the benefit of WHO prequalification is to verify that products are suitable for the populations in LMIC countries. Moreover, WHO prequalification also helps to increase standards for vaccine manufacturers in LMIC. The manufacturers of pharmaceutical products from middle-income countries (MIC) that involves in WHO prequalification is continually increasing, indicating that ability of LMIC production. Currently, LMIC account for over 40% of all prequalified medicine manufacturers and 50% of prequalified vaccines manufacturers (48).

2.6.2 The Vaccine Prequalification Program

The vaccine prequalification program aims to ensure that the vaccine supplied by UN procurement agencies meet quality, efficacy and safety requirement to use in the NIPs.

The vaccine prequalification program is used to assess procure eligible vaccine and follow the quality, safety, and efficacy of vaccines that supplies to receiving countries (4). Consequently, Immunization program managers can prepare, select and procure appropriate products so that more people can be vaccinated with safe, effective and quality vaccines(49).

The WHO-Prequalification indicates that the vaccines have quality, safety and efficacy WHO standards, is appropriate for the target population and meet the specifications of UN organizations for procuring that vaccine (50). The coverage of vaccine prequalification is all routine immunization for the prevention of 24 priority diseases. (48)

Vaccines, procured through this program to use in NIP, need to meet 3 requirements, including a registration in the countries where the vaccine is manufactured, WHO prequalification program, and local registration in the receiving countries. (4)

2.6.3 The vaccine registration

There is a three-step vaccine registration process in low-middle income countries or developing countries.

The first step is the first registration in the country where the vaccine is produced after the research and development of vaccines. The novel vaccines typically registered first from a Stringent Regulatory Authority (SRA) which is national regulatory authority in high income countries. In high income countries, the registration process and requirement are aligned between countries due to the development of International Conference on Harmonization of Technical Requirements for Registration of

Pharmaceuticals for Human Use (ICH). The ICH has promoted a Common Technical Document (CTD) for use in the ICH countries including EU, the US, Japan and South Korea to reduce resources and time and avoid redundancy. (4) Therefore, the vaccine registration in high income countries is faster than those in low and middle income countries. However, there is an increasing number of first vaccine registration from non-SRAs such as India.(51)

The second step is a WHO prequalification. WHO prequalification is the procedure to ensure that medicinal products with international quality, safety, and efficacy standards. It functions as a communication center between regulatory authorities and manufactures. PQ assessment also increases affordable vaccines and health products in low-middle income countries.(51) The first and second step can be conducted together. In practice, the manufacturers submit the similar submission process for registration vaccine twice in the first registration and WHO prequalification. This duplicative registration process increases the number of dossiers for the same vaccine which incur additional cost and delay vaccine access for some populations (4). The study by Ahonkhai et al.(14) divided vaccines based on their registration paths including products that first approved in SRA first in high income countries and those that first approved in a low-middle income countries National Regulatory Authority (Non-SRA first). The results demonstrated that the median times of WHO prequalification process for vaccines that have been approved in SRA first and non-SRA first are not different (16 months) due to the duplication of reviews for vaccines by

WHO Prequalification team. While the PQ process for drugs, that have been approved by SRA first, was shorter than those approved by non-SRA first.

The last step is registration with national regulatory authorities. All vaccines and medicinal products require local registration to confirm the efficacy, safety and quality of products. The duplicative registration process can occur in this step again due to different national requirements, especially in low-middle income countries. However, WHO introduced the Vaccine Expedited Review registration procedure for low-middle income countries in 2010 to accelerate the local registration process by allowing national regulatory authorities to access to prequalification assessment report and in turn, the national regulatory authorities have to give a approval decision within 90 days. (51)

The regulation of vaccine needs a regulatory system and specific regulatory functions defied by WHO including marketing authorization and facility licensing, Pharmacovigilance, NRA lot releases, laboratory access, regulatory inspections, and authorization, and monitoring of clinical trials. The functions depend on the vaccine source that countries purchasing through. If the purchase is made through UN procurement agencies, WHO recommends only the two functions including, marketing authorization and pharmacovigilance. If the purchase is made directly through international tenders by the non-producing countries of the certain vaccines, WHO recommends fulfilling two additional functions, including lot release and laboratory access (52).

2.6.4 Stringent Regulatory Authorities

The stringent regulatory authority (SRA) is the national regulatory agencies which are members or observers, or associates of the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use including (53)

The list was created by WHO Secretariat and the Global Fund to Fight AIDS, Tuberculosis and Malaria to help medicine procurement decisions. SRA is generally accepted by the international regulatory and procurement community(53).

The SRA have more facilities and experts to review vaccines for marketing authorization compared to non-SRA. Therefore, the marketing authorization in SRA usually faster than non-SRA and their people can get access to vaccine faster.

2.7 Vaccine research and development in Asia-Pacific region

The Developing Countries Vaccine Manufacturers Network (DCVMN) is an international alliance of vaccine manufacturers in developing countries to improve the capacity of these manufacturers in co-development of vaccines, knowledge exchange and conferences, supporting technology transfer, innovative research, and public information in the availability, safety and efficacy of vaccine, manufactured from developing-country countries.The purpose of this alliance is to produce and provide high-quality and affordable price vaccines to all population, especially for people in developing countries who have

high risk of vaccine protectable diseases but have low purchasing power. The network has 43 corporate members in 14 countries in Latin America, the Middle East and Africa, and the Asia-Pacific region including Argentina, Bangladesh, Brazil, China, India, Indonesia, Mexico, Pakistan, Republic of Korea, Russia, South Africa, Taiwan, Thailand, Vietnam (54–56)

2.8 Approval lag

After thalidomide tragedy in 1962, the US FDA introduced the assessment process to evaluate drug efficacy and safety, the process increased the time to approved drug (57). A drug lag or approval lag is a delay in drug availability for patients in a certain country. It includes absolute approval lag and relative approval lag. The absolute approval lag is a measure of product availability by comparing the number of product available in various countries. The relative approval lag is a measure of lag time between the approval date of the country of interest and the first global approval date. (58,59).

2.9 Previous studies

Kataria, et al (7) assessed the approval lag for new cardiovascular medicines in India compared with US and EU between 1999 and 2011. In India, access to new cardiovascular medicines was delayed due to a long approval process. The assessment of drug lag will give important information to resolve this problem. The results showed that the median approval lag for India was longer compare to the US and EU (median 44.14 months vs 0 and 2.99 months, respectively). This finding confirmed the approval lag for new cardiovascular medicines in India compared with the US and EU, resulted in the delay

access to new cardiovascular medicines in India. However, the possible reasons behind the approval lag and the impact of approval lag have not been analyzed in this study. (7)

Kataria, et al (60) assessed approval lag for new antineoplastic and immunomodulating medicines between India and the US and EU from 2011 to 2015, due to the rapid growth of cancer drugs over the past years. The results found that the median approval lag in India was longer compare to the US and EU (median 18.36 months vs 0 and 6.02 months, respectively). This confirmed that the drug lag in cancer therapies have existed in India. The possible reasons for drug lag are a delay in research and development, the submission from the pharmaceutical companies, and review processes. Future studies should analyze the background reason and impact of drug lag of cancer therapies in India. (60)

Okabayashi, et al (61) compared approval lag for inflammatory bowel disease (IBD) medicines between Asia (Japan, China, South Korea, Taiwan, and the Philippines) and the US and EU. The result found approval lag in Asia countries compared to the US and EU. However, the drug lag for IBD in Asia was decreasing due to the start of the biologic's era. (61)

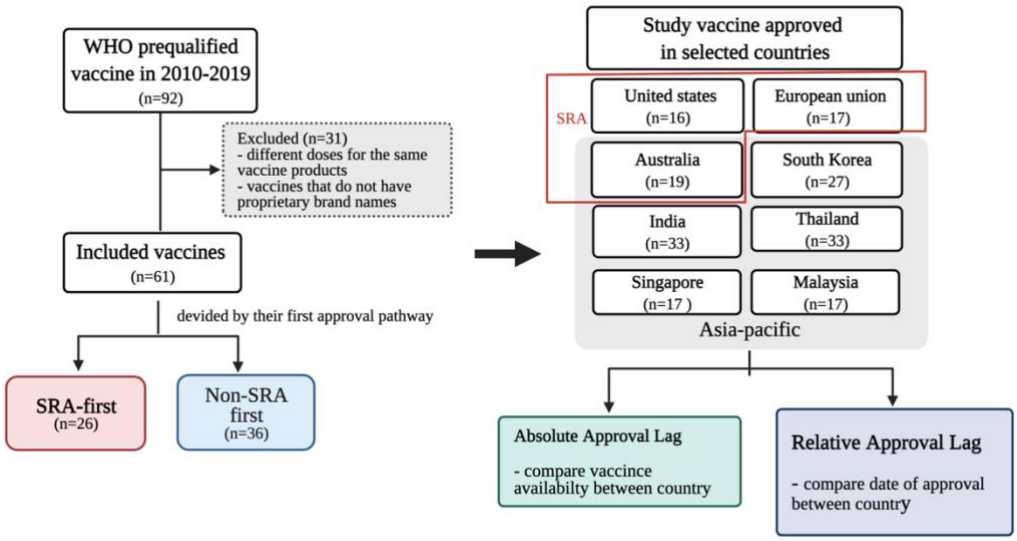
Lee, et al (6) compared approval lag in Korea and Japan from 2009 to 2017. The approval lag was found in Korea and Japan with the shorter lag in Korea than in Japan (median 28.2 vs 54.1 months). The approval lag factors had been assessed. The variable original date and domestic company were both associated with the median approval lag in Korea. In Japan, the initial approval date and orphan drugs were both associated with

median approval lag. The authors suggest that the shorter drug lag in Korea could be explained by the previous understanding in new drug development. The percentage of global clinical trials in Korea is higher than in Japan. Inclusion in global clinical trials is important in clinical development strategy to decrease drug lag. (6)

III. Methods

3.1 Data sources and data collection

Figure 1 shows a flow diagram of methods



Note: SRA; stringent regulatory authority

This study used WHO prequalified vaccines as study vaccines because WHO prequalification indicates that vaccines meet international standards of quality, safety and efficacy. WHO list of prequalified vaccine also covers all vaccines required for routine immunization against 24 priority diseases.

The definition of stringent regulatory authorities (SRAs) by World Health Organization (WHO) was used in this study. SRA means a A regulatory authority which is the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) member, observer, or a regulatory authority associated with an ICH member(12), including Australia, Austria, Belgium, Bulgaria, Canada, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Kingdom and United States of America.(53) Using this definition of SRAs, one SRAs in Asia-pacific countries, i.e. and Therapeutics Goods Administration (TGA) of Australia, were included in this study. The United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA), which are SRAs in the US and EU, were used in this study as reference countries.

The regional authorities or non-SRA in this study were purposively selected included Ministry of Food and Drug Safety (MDFS) of South Korea, Central Drugs Standard Control Organization (CDSCO) of India, Thai Food and Drug Administration (Thai FDA) of Thailand, National Pharmaceutical Control Bureau (NPCB) of Malaysia and Health Sciences Authority (HAS) of Singapore.

We collected information of vaccines, which were prequalified by WHO, between 2010 January 01 and 2019 December 2019. Information about commercial name, vaccine type and date of prequalification was retrieved from WHO website. Information about date

of approval of WHO prequalified vaccine in selected Asia-Pacific countries, US FDA and EMA was retrieved from the official website of drug approval agency for each country (Table 4).

Table 4 data sources

Region	**Country**	**Regulatory Agency**	**Data sources**
North America Europe	United States	US Food and Drug Administration (FDA)	The Center for Biologics Evaluation and Research (CBER), Vaccines Licensed for Use in the United States: https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states (62)
	European Unions	European Medicines Agency (EMA)	Committee for Medicinal Products for Human Use (CHMP), The European Public Assessment Report (EPAR): https://www.ema.europa.eu/en (63)
	Australia	Therapeutic Goods Administration (TGA)	the Australian Register of Therapeutic Goods (ARTG).; Australia: https://tga-search.clients.funnelback.com/s/search.html?query=&collection=tga-artg (64)

South Asia	India	The Central Drugs Standard Control Organization (CDSCO)	Vaccines, SmPC; https://cdsco.gov.in/opencms/opencms/en/biologicals/Vaccines/ (65)
East Asia	South Korea	Ministry of Food and Drug Safety	Drug search; https://nedrug.mfds.go.kr/searchDrug (66)
South East Asia	Thailand	Thai Food and Drug Administration	Product search; https://porta.fda.moph.go.th/FDA_SEARCH_ALL/MAIN/SEARCH_CENTER_MAIN.aspx (67)
	Singapore	Health Sciences Authority (HSA)	Listing of Registered Therapeutic: https://data.gov.sg/dataset/listing-of-registered-therapeutic-products (68)
	Malaysia	National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia	Malaysia Drug Control Authority, Product search: https://www.npra.gov.my/index.php/en/(69)

There were pre-qualified 92 vaccines between January 01, 2010 and December 31, 2019. We excluded different doses for the same vaccine products and used the

fastest prequalified date among different doses for the same vaccine. We excluded vaccines that do not have proprietary brand names because of the difficulty encountered in collecting approval data and approved dates. Ultimately, 61 vaccines were evaluated and they were divided into two groups based on their first approval pathway, i.e., vaccines that first approved by SRA (SRA first) and those that first approved by non-SRA (non-SRA first).

3.2 Vaccine Approval Date

The vaccine approval date refers to the date of approval by the national regulatory authority, including US FDA, EMA in the EU, TGA in Australia, CDSCO in India, MFDS in South Korea, Thai FDA in Thailand, HSA in Singapore and NPRA in Malaysia.

3.3 Comparison of Approval lag between countries

We analyzed the approval lag in terms of 'absolute approval lag' and 'relative approval lag'. Absolute approval lag is the proportion of approved vaccines in each country out of all studied vaccines. Relative approval lag is the lag time between the approval date in country of interest and the first global approval date.(61)

3.4 Statistical analysis

Because the median is less sensitive to extreme values than the mean, it was used to calculate relative approval lag. (6) Man-Whitney U Test was used to examine the statistical difference between relative approval lag between SRA first and non-SRA first

group, and a p-value of ≤0.05 indicated statistical significance. SPSS version 25 was used for statistical analysis.

IV. Results

4.1 The characteristics of study vaccines

Characteristics of WHO-prequalified vaccines are summarized in Table 3. Total of 61 WHO-prequalified vaccines were included in the analysis, among which 15 vaccines (24.6%) are influenza vaccines and 9 (14.8%) are Diphtheria-Tetanus-Pertussis. More than half of vaccines were first licensed by Non-SRAs, with 21 (34.4%) of WHO-prequalified vaccines approved by the CDSCO of India and 10 vaccines (16.4%) approved by the MFDS of South Korea. Approximately 42.6% of WHO-prequalified vaccines was approved in SRA first, including 14 vaccines (23%) by the US FDA and 12 vaccines (19.7%) by EMA and EU countries (Table 5).

Table 5 characteristics of WHO-Prequalified vaccines between 2010-2019 (n=61)

	Total	
Variables	**n**	**%**
Total	61	100
First approval country		
Stringent Regulatory Authoritiy first	26	42.6
United States	14	23.0
European Union	12	19.7
Non-Stringent Regulatory Authority first	35	57.4
India	21	34.4
Korea	10	16.4
China	1	1.6
Thailand	1	1.6
Indonesia	1	1.6
Cuba	1	1.6
Vaccine type		

	Cholera	3	4.9
	Diphtheria-Tetanus	1	1.6
	Diphtheria-Tetanus-Pertussis	9	14.8
	Ebola	1	1.6
	Haemophilus influenzae type b	1	1.6
	Hepatitis A	3	4.9
	Human Papillomavirus	1	1.6
	Influenza	15	24.6
	Japanese Encephalitis	2	3.3
	Measles, Mumps and Rubella	1	1.6
	Meningococcal	5	8.2
	Pneumococcal	3	4.9
	Polio	6	9.8
	Rabies	3	4.9
	Rotavirus	3	4.9
	Tetanus	1	1.6
	Typhoid	2	3.3
	Varicella	2	3.3
Year			
	2010	9	14.8
	2011	6	9.8
	2012	3	4.9
	2013	6	9.8
	2014	7	11.5
	2015	5	8.2
	2016	4	6.6
	2017	4	6.6
	2018	9	14.8
	2019	8	13.1

4.2 Absolute approval lag

The absolute approval lag of WHO-prequalified vaccines are shown in Table 4. Half of WHO-prequalified vaccines were approved in Thailand (33 vaccines, 54%) and India (33 vaccines, in 54%), followed by South Korea (27 vaccines, 44%). The majority of Asian countries approved more WHO pre-qualified vaccines than the US and EU. The US approved WHO pre-qualified vaccines only from SRA first, whereas other countries approved vaccines from both SRA first and Non-SRA first.

Vaccines firstly approved and manufactured in the US or EU are available in all selected countries, those approved and manufactured in India are available in all selected Asian countries and EU, and those approved and manufactured in South Korea were licensed only in its own country and ASEAN, including Thailand, Singapore, Malaysia.

Diphtheria-Tetanus-Pertussis, Hepatitis A, Influenza A Meningococcal, Pneumococcal and Rotavirus vaccines were licensed in all selected countries. Among all vaccine types, Influenza vaccines accounted for the largest proportion of WHO-preqaulified vaccines (15 vaccines, 24.6%). South Korea approved 60% of WHO-prequalified influenza vaccines (9 vaccines, 15%). Ebola vaccine was only approved in the US and EU while Japanese Encephalitis vaccines were only approved in Asian Countries (Table 6).

Table 6 Absolute approval lag of WHO-prequalified vaccine divided by First approval country and vaccine type (n=61)

	Total		US		EU		Australia		India		South Korea		Thailand		Singapore		Malaysia	
Variables	n	(%)	**n**	(%)	**n**	(%)	**n**	(%)	**n**	(%)	**n**	(%)	**n**	(%)	**n**	(%)	**n**	(%)
Total	**61**	(100)	**16**	(26)	**17**	(28)	**19**	(31)	**33**	(54)	**27**	(44)	**33**	(54)	**17**	(28)	**17**	(28)
First approval			**14**	(23)	**12**	(20)	**0**	(0)	**21**	(34)	**10**	(16)	**1**	(1.6)	**0**	(0)	**0**	(0)
Divided by first approval NRAs																		
SRA first	**26**	(42.6)																
US	**14**	(23.0)	**12**	(20)	**6**	(9.8)	**11**	(18)	**5**	(8.2)	**9**	(15	**10**	(16)	**10**	(16)	**8**	(13)
EU	**12**	(19.7)	**4**	(6.6)	**8**	(13)	**7**	(11)	**7**	(11)	**7**	(11)	**7**	(11)	**5**	(8.2)	**6**	(9.8)
Non-SRA first	**35**	(57.4)																
India	**21**	(34.4)	**0**	(0)	**3**	(4.9)	**1**	(1.6)	**21**	(34)	**1**	(1.6)	**9**	15	**1**	(1.6)	**1**	(1.6)
Korea	**10**	(16.4)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**10**	(16)	**4**	(6.6)	**1**	(1.6)	**2**	(3.3)
China	**1**	(1.6)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**1**	(1.6)	**0**	(0)	**0**	(0)
Thailand	**1**	(1.6)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**1**	(1.6)	**0**	(0)	**0**	(0)
Indonesia	**1**	(1.6)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**1**	(1.6)	**0**	(0)	**0**	(0)
Cuba	**1**	(1.6)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)
Divided by Vaccine type																		
Cholera	**3**	(4.9)	**0**	(0)	**1**	(1.6)	**0**	(0)	**1**	(1.6)	**2**	(3.3)	**1**	(1.6)	**0**	(0)	**1**	(1.6)
Diphtheria-Tetanus	**1**	(1.6)	**0**	(0)	**0**	(0)	**0**	(0)	**1**	(1.6)	**0**	(0)	**1**	(1.6)	**0**	(0)	**0**	(0)
Diphtheria-Tetanus-Pertussis	**9**	(14.8)	**2**	(3.3)	**2**	(3.3)	**3**	(4.9)	**7**	(11)	**4**	(6.6)	**8**	(13)	**3**	(4.9)	**3**	(4.9)
Ebola	**1**	(1.6)	**1**	(1.6)	**1**	(1.6)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)
Haemophilus influenzae type b	**1**	(1.6)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)	**0**	(0)
Hepatitis A	**3**	(4.9)	**2**	(3.3)	**2**	(12	**2**	(3.3)	**2**	(3.3)	**1**	(1.6)	**2**	(3.3)	**2**	(3.3)	**2**	(3.3)
Human Papillomavirus	**1**	(1.6)	**1**	(1.6)	**1**	(1.6)	**1**	(1.6)	**0**	(0)	**1**	(1.6)	**1**	(1.6)	**1**	(1.6)	**1**	(1.6)

Influenza	**15**	(24.6)	**4**	(6.6)	**1**	(1.6)	**3**	(4.9)	**3**	(4.9)	**9**	(15)	**6**	(9.8)	**2**	(3.3)	**1**	(1.6)
Japanese Encephalitis	**2**	(3.3)	**0**	(0)	**0**	(0)	**0**	(0)	**1**	(1.6)	**0**	(0)	**1**	(1.6)	**0**	(0)	**0**	(0)
Measles, Mumps and Rubella	**1**	(1.6)	**0**	(0)	**1**	(1.6)	**1**	(1.6)	**1**	(1.6)	**1**	(1.6)	**1**	(1.6)	**0**	(0)	**1**	(1.6)
Meningococcal	**5**	(8.2)	**2**	(3.3)	**2**	(3.3)	**3**	(4.9)	**3**	(4.9)	**2**	(3.3)	**3**	(4.9)	**3**	(4.9)	**3**	(4.9)
Pneumococcal	**3**	(4.9)	**1**	(1.6)	**2**	(3.3)	**2**	(3.3)	**3**	(4.9)	**2**	(3.3)	**1**	(1.6)	**2**	(3.3)	**3**	(4.9)
Polio	**6**	(9.8)	**0**	(0)	**3**	(4.9)	**0**	(0)	**4**	(6.6)	**2**	(3.3)	**1**	(1.6)	**0**	(0)	**0**	(0)
Rabies	**3**	(4.9)	**0**	(0)	**0**	(0)	**1**	(1.6)	**3**	(4.9)	**0**	(0)	**2**	(3.3)	**1**	(1.6)	**0**	(0)
Rotavirus	**3**	(4.9)	**1**	(1.6)	**1**	(1.6)	**1**	(1.6)	**3**	(4.9)	**1**	(1.6)	**2**	(3.3)	**1**	(1.6)	**1**	(1.6)
Tetanus	**1**	(1.6)	**0**	(0)	**0**	(0)	**0**	(0)	**1**	(1.6)	**0**	(0)	**1**	(1.6)	**0**	(0)	**0**	(0)
Typhoid	**2**	(3.3)	**1**	(1.6)	**0**	(0)	**1**	(1.6)	**1**	(1.6)	**0**	(0)	**1**	(1.6)	**1**	(1.6)	**0**	(0)
Varicella	**2**	(3.3)	**1**	(1.6)	**0**	(0)	**1**	(1.6)	**0**	(0)	**2**	(3.3)	**1**	(1.6)	**1**	(1.6)	**1**	(1.6)

4.2 Relative approval lag

Relative approval lag of WHO PQ vaccines is summarized in Figures 2 and 3. Among all countries, Malaysia has the longest approval lag with 161 months from the world first approval date. Relative approval lag of SRA first vaccines was also the longest in Malaysia with 161 months but the shortest in the US and EU with 0 months (Figure 2).

Table 7 Relative approval lag for WHO pre-qualified vaccines divided by the first approval NRAs. (n=61)

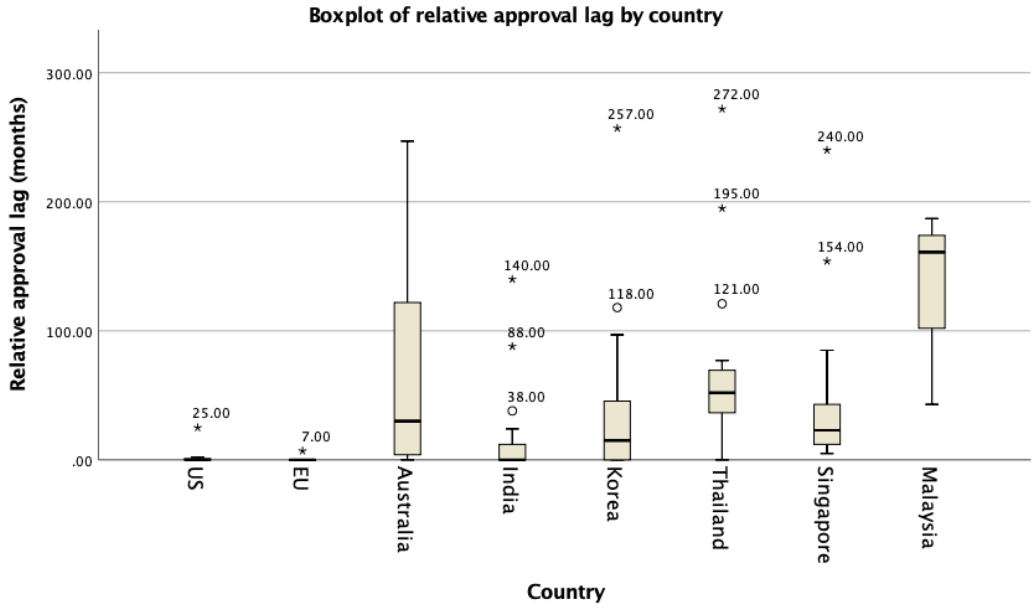
	Median relative approval lag [a], months (range)							
	US (n=13)	EU (n=7)	Australia (n=16)	India (n=17)	South Korea (n=23)	Thailand (n=24)	Singapore (n=14)	Malaysia (n=3)
All vaccines	0 (0-25)	0 (0-7)	30 (0-247)	0 (0-140)	15 (0-257)	52 (0-272)	23 (5-240)	161 (43-187)
SRA first	0 (0-25)	0 (0-7)	30 (0-247)	38 (12-140)	43 (3-257)	47 (5-240)	23 (5-240)	161 (43-187)
Non-SRA first	na	na	na	0 (0-0)	0 (0-37)	55 (0-195)	na	na
P-value [b]								
Median	na	na	na	.000*	.036*	1	na	na

[a] Relative approval lag: an lag time in approval in a certain country after 1st approval date

[b] P values were derived using Man-Whitney U test to examine the statistical difference between relative approval lag between SRA first and non-SRA first group and a p-value of ≤ 0.05 indicates statistical significance with 95% CIs.

na: not applicable due to the date limitation

Figure 2 shows Boxplot of vaccine approval lag



Among Non-SRA first vaccines, the longest approval lag was 55 months in Thailand. The differences in median and distribution approval lag between SRA first vaccines and Non-SRA first vaccines were statistically significant in South Korea and India (p-values <0.05) (Figure 3).

Relative approval lag of WHO prequalified vaccines by vaccine type is shown in Figure 4. Among all vaccine type, Varicella vaccines have the longest median approval lag with 0- 272 months (Figure 4).

Figure 3 shows boxplot of vaccine approval lag divided by the first approval NRAs.

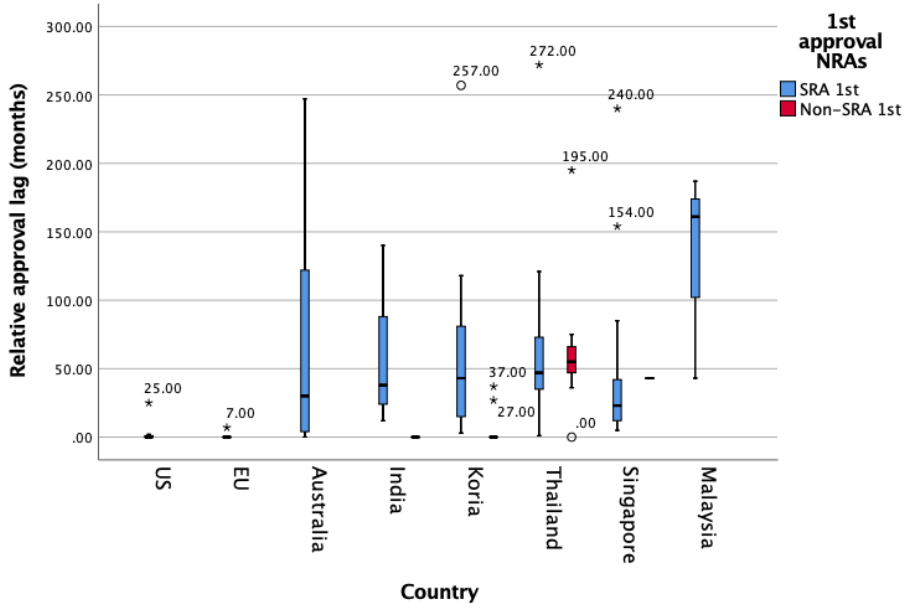


Figure 4 shows Clustered boxplot of vaccine approval lag divided by vaccine types.

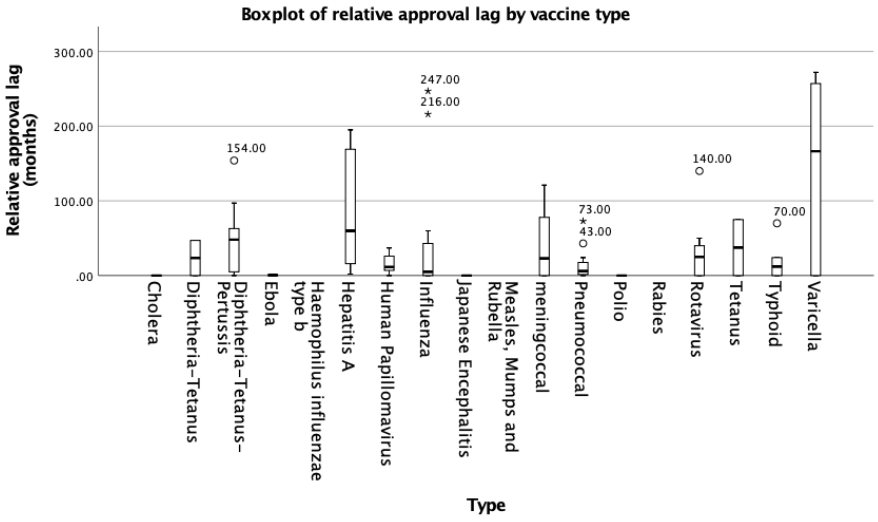


Table 8 Relative approval lag for WHO prequalified vaccines divided by vaccine types

	Median approval lag, months (range)							
Vaccine type	**US**	**EU**	**Australia**	**India**	**South Korea**	**Thailand**	**Singapore**	**Malaysia**
Cholera	-	na	-	na	0	na	-	-
Diphtheria-Tetanus	-	-	-	0	-	47	-	-
Diphtheria-Tetanus-			17.5		48	61.6	98	
Pertussis	0	-	(5-30)	0	(0-97)	(54-66)	(42-154)	-
Ebola	1	0	-	-	-		-	-
			164	25		117	16	174
Hepatitis A	2	na	(151-177)	(12-38)	81	(39-195)	(15-17)	(161-187)
Human Papillomavirus	0	7	8	-	15	37	26	-
	0		216	0	5	35.5	24	
Influenza	(0-1)	-	(0-247)	(0-0)	(0-59)	(1-60)	(5-43)	-
Japanese Encephalitis	-	-	-	0		0	-	-
Measles, Mumps and								
Rubella	-	na	na	na	na	na	-	na

	0	0	16	44	72.5	77	23	
Meningococcal	(0-0)	(0-0)	(3-78)	(0-88)	(27-118)	(61-121)	(23-85)	-
		0	1.5		7		8.5	
Pneumococcal	na	(0-0)	(0-3)	24	(3-11)	73	(6-11)	43
				0				
Polio	-	na	na	(0-0)	na	na	-	-
Rabies	-	-	na	na	-	na	na	-
				0		45		
Rotavirus	25	0	30	(0-140)	24	(40-50)	na	-
Tetanus	-	-	-	0	-	75	-	-
Typhoid	0	-	70	0	-	24	12	-
					128.5			
Varicella	0	-	93	-	(0-257)	272	240	-

na: vaccine is available in certain country but the approval date is not available to assess approval lag

V. Discussions

This study aims to evaluate the availability of vaccines and the delay in access to vaccines in Asia-Pacific countries. We assessed vaccines that were prequalified by WHO between 2010 and 2019. Total of 61 WHO-prequalified vaccines were included in the analysis and were divided into two groups based on their first approval pathway, SRA first and non-SRA first. The availability of vaccines and the delay in access to vaccine were compared among Asia-Pacific countries, the US, and EU

5.1 The characteristics of study vaccines

Our results found that the proportion of non-SRA first vaccines were over 50% of WHO-prequalified vaccines with 34.4% and 16.4% firstly approved by India and South Korea, respectively. Usually, the vaccine manufacturing country is the first country approving the vaccines. India and South Korea are in the Developing Countries Vaccine Manufacturers Network (DCVMN), which have capacity to manufacture and supply vaccines with high quality and affordable prices to developing countries (56) which is the target countries of WHO prequalified vaccines. According to WHO reports, the developing countries' manufacturers account for more than 50% of the production of prequalified vaccines. (48). According to 2019 WHO Global Vaccine Market Report (70), DCVMs hold the largest share of WHO prequalified vaccines with over 65% in all region except the EU. India are the major DCVM in all regions.(70)

5.2 Vaccine availability

For the availability or absolute approval lag of WHO prequalified vaccine, our study showed that the number of study vaccines available in selected countries in Asia-Pacific region was more than those in the US and EU. More than 50% WHO prequalified vaccines are available in Thailand (54%) and India (54%), followed by 44 % in South Korea.

WHO prequalified vaccines contained both innovator vaccines with high price from the US and EU and more affordable price vaccines from South Korea and India. Middle-income country, such as Thailand and India, have limited financial resources for adding pharmaceutical products into their universal healthcare coverage.(71) In Thailand, most pharmaceutical products covered in universal healthcare coverage in public sectors are locally produced products and affordable price products from other countries. While innovator products are mainly used in private sectors by self-purchase. Due to the difference in wealthy and poverty parts of the population, the availability of both innovator vaccines and affordable price vaccines in the country is important to increase access to vaccines in public sectors and to be alternatives for private sectors.(72) On the other hand, high-income countries, such as Australia and the countries in EU, can afford innovator products and have sufficient financial funding for the inclusion of innovator vaccines in their universal healthcare coverage or insurance with the less demand of alternative vaccines.

In this study, we also found that vaccines manufactured in the US or EU were available in all selected countries, those manufactured in India were available in all selected Asian countries and EU, and those manufactured in South Korea were licensed only in its own country and ASEAN, including Thailand, Singapore, Malaysia. The differences in requirements and registration process between the country may also hold an essential role in the availability of vaccines. National regulatory agencies in the US, EU and Australia are the stringent regulatory authoritys (SRA). The vaccines from India and South Korea, which is non-SRA, may have difficulties to get approved by SRA due to the strict requirements and registration process.

In the results, Influenza vaccines accounted for the largest proportion of WHO-preqaulified vaccines due to the constant change of influenza viruses. Influenza vaccine compositions need to be reviewed every year, based on the viruses that may be the most prevalent for the upcoming flu season. (22,73) The result showed that Ebola vaccine was only approved in the US and EU while Japanese Encephalitis vaccines were only approved in Asian Countries. The largest Ebola outbreak occurred in West Africa in 2014-2015. The Ebola virus disease cases had been imported to the US and EU through infected travelers and transmitted the disease to domestic healthcare workers. Therefore, the Ebola vaccine was approved in the US and EU to prevent the importation of Ebola virus disease from an epidermic region.(15,16) While endemic Japanese encephalitis virus transmission occurs in South-East Asia and Western Pacific regions. WHO recommends that endemic countries should introduce JE vaccination schedules. (23) The several Asia-pacific countries, the

endemic region of Japanese encephalitis virus, had been approved to Japanese Encephalitis vaccines to use in their countries. South Korea, India, Thailand and Malaysia also included Japanese Encephalitis vaccines in their national immunization program.

5.3 Delay in vaccine access

Our results demonstrated that Malaysia had the longest approval lag with 161 months from the world first approval date. Relative approval lag of SRA first vaccines was also the longest in Malaysia with 161 months. These results might be due to the limitation of access to approval date data in Malaysia. Only 3 vaccines have approval date provided on Malaysia' NRA official websites. Therefore, these 3 vaccines might not be able to represent relative drug lag in Malaysia.

Our finding that the longer approval lag in Asia-Pacific countries, compared to the US and EU, were consistent with previous studies that assessed the approval lag in cancer drug(60), inflammatory bowel disease drug (61) and cardiovascular drug (7). Kataria, et al (60) compared approval lag for cancer drugs between India and the US and EU and confirmed the approval lag for cancer drugs in India. This drug lag may result from a delay in research and development, the submission from the pharmaceutical companies, and review process by India' s national regulatory authority. Okabayashi, et al (61) compared approval lag for inflammatory bowel disease (IBD) drugs between Asia (Japan, China, South Korea, Taiwan, and the Philippines) and the US and EU and found the drug lag for IBD in Asian countries, compared to the US and EU. However, the approval lag for IBD in Asia is decreasing due to the start of the biologic's era. Kataria et al (7) assessed the

approval lag for new cardiovascular medicines between India and the US or EU and confirmed approval lag in new cardiovascular medicines in India, compared with the US and EU, resulted in the delay to access to new cardiovascular drug in India.

The approval lag of vaccine in Asia-Pacific may be because of the differences of vaccine's regulatory requirements and registration processes in Asia-Pacific countries, compared to the US and EU. South Korea requires local clinical study data for review of safety and efficacy of biological products, including vaccines.(74) Local clinical data help to identify racial differences and establish the optimal dosage(75), but it takes time to conduct the local clinical trial and delays the approval of vaccines in the Korea. However, global clinical trials can eliminate the need of conducting the new local clinical trial for approval.(61) In past decades, the conduction of global clinical trials in Korea has grown rapidly and the Korean government also supports nationwide clinical trials by establishing Korea Good Clinical Practice (KGCP)and Korean National Enterprise for Clinical Trials (KoNECT) for Clinical Trials, this might help reduce drug approval lag. (76,77)

Southeast Asian countries, such as Thailand, Malaysia and Singapore, use ASEAN (the Association of Southeast Asian Nations) Common Technical Dossier (CTD) format (78,79), which aims to streamline regulatory requirements between countries and regions to preserve resources and time and avoid redundancy in ASEAN.(1) Dellepiane N, et al (4) compared the CTD numbering structure and contents for vaccine registration from PAHO (the Pan-American Health Organization), India, Jordan, ASEAN and Thailand with ICH CTD, which commonly uses in ICH member countries including the US, EU, Australia and

South Korea. The comparison between the ASEAN and the ICH CTD revealed 93% of similarity, but 100% differences in numbering because the dossier structures are different. Thailand CTD does not fully comply with the ASEAN CTD. The comparison between Thailand CTD and ICH CTD showed only 25% similarity for content and 75% difference in numbering. The comparison between India CTD and ICH CTD showed 24% similarity in contents and 83% difference in numbering. The difference in these CTDs, compared to ICH CTD, may be one of contributing factors for the vaccine approval lag, especially for Thailand CTD that is different in contents and numbering from ASEAN CTD and ICH CTD. The difference in content requirement has influence on the registration timeline, pharmaceutical companies need more time to prepare a country specific CTD for vaccine registration, leading to unnecessary efforts, prolonged approval procedures and delay in vaccine access.(4)

The differences in relative approval lag between SRA first and non-SRA first group were examined only in India, South Korea and Thailand because non-SRA first vaccines do not available in the US and the lack of approval date data of the non-SRA first vaccine in other countries. Our finding showed that the difference between relative approval lag between SRA first and non-SRA first group in South Korean and India was statistically significant. The approval lag in non-SRA first group in South Korea and India was shorter than those in SRA group (median 0 vs 43 months, P=0.036; 0 vs 38 months, P=0.0001, respectively). This may be because all non-SRA first vaccines in South Korea and India was firstly approved in their own countries, so there was no approval lag for non-

SRA. While there was approval lag in SRA first vaccines because they were approved from outside South Korea and India. This requires time to prepare country-specific dossiers for submission. Moreover, Korea requires local data in South Korea before approval.

On the other hand, the approval lag in SRA first group in Thailand is shorter than those in Non-SRA first group (median 0 vs 43 months). This may be because the SRA is more strict in requirements and review for approval than non-SRA and , in Thailand, the pharmaceutical product ,which have already been approved by SRA, can use accelerated process to speed registration of vaccines. (80) The findings were comparable to previous study by Ahonkhai et al.(14). They divided vaccines based on their first approval paths including products that first approved in SRA (SRA first) and those that first approved in other National Regulatory Authority (Non-SRA first) and compared approval time of medicines and vaccines in Sub-Sahara Africa. The approval time of drugs, which have been approved by SRA first, was shorter than those approved by non-SRA first (median 11 vs 18 months)

Among all vaccine type, Varicella vaccines had the longest median approval lag. Compared to Asia-Pacific countries, the US and EU approved vaccines faster in all type of vaccines. Varicella has a smallest market volume among other vaccine type (70). Varicella is a mild disease in healthy children, but it can cause severe and fatal complications.(34) However, The disease awareness of Varicella is low and also not received the significant global or regional attention, particularly in LMIC (81). In the selected Asian countries, only Australia, South Korea and Singapore have included varicella vaccine to their NIP with

publicly funding. While Thailand, Malaysia and India, which is middle-income country, had not added to the NIP due to the limited financial resources. Varicella vaccine is an optional vaccine in these countries.(82) The varicella vaccine is a target vaccine in Gavi's vaccine investment strategy.(35) The low public attention, low disease awareness, non-NIP vaccines in some countries, and the non-target vaccines in Gavi's strategy may be reasons for the longest approval lag of varicella vaccine among other vaccines. Goh, et al. (35) reviewed the varicella burden in the Asia-Pacific region and indicated a high disease burden in the region. The introduction of varicella in NIP can decrease the disease burden. Therefore, it is necessary to improve public awareness and attention of varicella and include varicella to NIP to reduce the disease burden. This may also improve the approval lag of varicella vaccine in Asia-pacific countries.

5.4 Limitations

Due to the difficulty in collecting vaccine approval data and approval date, some data may be missing, especially for Malaysia and India. These countries have no online searchable database for vaccines, the approval data from India was obtained from summary of product characteristics (SmPC) and the approval data from Malaysia was obtained from Registered Product List. The challenge in data collection resulted in the small sample size in the analysis. Therefore, the relative drug lag in some countries might not represent the actual relative drug lag in countries. The investigation of factors associated with the delays in approval of vaccines in Asia-pacific countries is not conducted in this study, due to the limitation of data available.

5.5 Implication

The data about the gaps in availability and the delay in approval of vaccine in Asia-pacific countries will help us better understand inequitable vaccine access. The data can be used to support the improvement of vaccine access by supporting call for financial and policy response to end the differences in vaccine access. However, it is necessary to analyze the factors associated with delay in vaccine access.

In COVID-19 pandemic, equitable access to safe and effective COVID-19 vaccines is a priority to end the COVID-19 crisis. Understanding the inequities in previous vaccine access in the region may help to support calls for more financial support for COVAX, a worldwide initiative supported by the Gavi, the Coalition for Epidemic Preparedness Innovations (CEPI) and WHO that intends to provide equitable access to COVID-19 vaccines

5.6 Conclusion

Vaccination is a cost-effective intervention and one of the most successful methods to prevent infectious disease and improve health status. Vaccine access can also save time and money and reduces the social and economic burden of the disease.

This study demonstrated the difference in vaccine availability in the Asia-Paficine countries and confirmed approval lag of vaccine in the Asia-pacific countries, compared to the US and EU, indicating a gap between Asia-pacific countries and the US and EU in regard to access to new vaccine. The gap in vaccine availability may be attributed to the incidence and disease burden, financial resources, and the inclusion in national immunization programs. The vaccine approval lag in Asia-Pacific countries may be attributed to the differences in vaccine development and registration process in between countries and region, low disease attention and awareness, low disease incidence and burden in the region, and the non-national immunization program vaccines.

Future studies need to analyze the background factors related to the gap in availability and vaccine approval lag in Asia-Pacific countries and assess the impact of vaccine approval lag in the region.

References

1. Tsai TF, Rao RDSV, Xu ZY. Immunization in the Asia-Pacific Region. In: Plotkin's Vaccines [Internet]. Elsevier; 2018 [cited 2020 Oct 13]. p. 1466-1485.e2. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7152242/
2. Estrada G, Han X, Park D, Tian S. AsIA's MIDDle-INCOMe ChAlleNge: AN OvervIew. 2017 [cited 2020 Dec 21]; Available from: http://dx.doi.org/10.22617/WPS179122-2
3. Larson HJ, Cooper LZ, Eskola J, Katz SL, Ratzan S. Addressing the vaccine confidence gap [Internet]. Vol. 378, The Lancet. Lancet Publishing Group; 2011 [cited 2020 Dec 21]. p. 526–35. Available from: https://pubmed.ncbi.nlm.nih.gov/21664679/
4. Dellepiane N, Pagliusi S. Challenges for the registration of vaccines in emerging countries: Differences in dossier requirements, application and evaluation processes. In: Vaccine [Internet]. Elsevier Ltd; 2018 [cited 2020 Oct 11]. p. 3389–96. Available from: /pmc/articles/PMC6278877/?report=abstract
5. Venkatakrishnan K, Burgess C, Gupta N, Suri A, Takubo T, Zhou X, et al. Toward Optimum Benefit-Risk and Reduced Access Lag For Cancer Drugs in Asia: A Global Development Framework Guided by Clinical Pharmacology Principles [Internet]. Vol. 9, Clinical and Translational Science. Blackwell Publishing Ltd; 2016 [cited 2020 Oct 6]. p. 9–22. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5351319/

6. Lee SW, Park SH, Song I, Noh Y, Park H, Ha D, et al. Notable Differences in Drug Lag Between Korea and Japan of New Drugs Between 2009 and 2017. Ther Innov Regul Sci. 2019;
7. Kataria BC, Mehta DS, Chhaiya SB. Drug lag for cardiovascular drug approvals in India compared with the US and EU approvals. Indian Heart J. 2013 Jan;65(1):24–9.
8. Vaccine-preventable diseases and vaccines 6.1 General considerations [Internet]. [cited 2021 Apr 11]. Available from: http://www.who.int/injection_safety/global-campaign/injection-safety_guidline.pdf,
9. Mihigo R, Okeibunor J, Cernuschi T, Petu A, Satoulou A, Zawaira F. Improving access to affordable vaccines for middle-income countries in the african region. Vaccine. 2019 May 9;37(21):2838–42.
10. Health AGD of. Vaccine Preventable Diseases.
11. St-Amant O, Lapum J, Dubey V, Beckermann K, Huang C-S, Weeks C, et al. What is a Vaccine-Preventable Disease (VPD)?
12. MODULE 1 – Vaccine-preventable diseases - WHO Vaccine Safety Basics [Internet]. [cited 2021 Apr 1]. Available from: https://vaccine-safety-training.org/vaccine-preventable-diseases.html
13. Standards S. Vaccine-Preventable Diseases [Internet]. [cited 2021 May 10]. Available from: http://www.who.int/cholera/task_force/GTFCC-
14. Ali M, Nelson AR, Lopez AL, Sack DA. Updated global burden of cholera in

endemic countries. PLoS Negl Trop Dis. 2015 Jun 4;9(6).

15. Ebola virus disease [Internet]. [cited 2021 May 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease
16. Ebola Vaccine: Information about Ervebo® | Clinicians | Ebola (Ebola Virus Disease) | CDC [Internet]. [cited 2021 May 10]. Available from: https://www.cdc.gov/vhf/ebola/clinicians/vaccine/index.html
17. WHO | Haemophilus influenzae type b (Hib). WHO. 2014;
18. Hepatitis A [Internet]. [cited 2021 May 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-a
19. Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, et al. HPV Vaccination and the Risk of Invasive Cervical Cancer. N Engl J Med. 2020 Oct 1;383(14):1340–8.
20. WHO | Disease burden and mortality estimates. WHO [Internet]. 2019 [cited 2021 May 10]; Available from: http://www.who.int/healthinfo/global_burden_disease/estimates/en/
21. SEASONAL INFLUENZA VACCINES: An overview for decision-makers.
22. Key Facts About Seasonal Flu Vaccine | CDC [Internet]. [cited 2021 May 10]. Available from: https://www.cdc.gov/flu/prevent/keyfacts.htm
23. Japanese encephalitis [Internet]. [cited 2021 May 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/japanese-encephalitis
24. Measles [Internet]. [cited 2021 May 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/measles

25. Meningococcal meningitis [Internet]. [cited 2021 May 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/meningococcal-meningitis

26. Pneumonia [Internet]. [cited 2021 May 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/pneumonia

27. O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet [Internet]. 2009 [cited 2021 May 20];374(9693):893–902. Available from: https://pubmed.ncbi.nlm.nih.gov/19748398/

28. Poliomyelitis [Internet]. [cited 2021 May 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/poliomyelitis

29. Rabies [Internet]. [cited 2021 May 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/rabies

30. WHO | Rotavirus. WHO [Internet]. 2020 [cited 2021 Jun 3]; Available from: http://www.who.int/immunization/diseases/rotavirus/en/

31. Tetanus [Internet]. [cited 2021 May 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/tetanus

32. Typhoid [Internet]. [cited 2021 May 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/typhoid

33. WHO | Varicella. WHO. 2015;

34. Standards S. Varicella Vaccine-Preventable Diseases.

35. Goh AEN, Choi EH, Chokephaibulkit K, Choudhury J, Kuter B, Lee PI, et al. Burden of varicella in the Asia-Pacific region: a systematic literature review [Internet]. Vol. 18, Expert Review of Vaccines. Taylor and Francis Ltd; 2019 [cited 2021 Apr 27]. p. 475–93. Available from: https://www.tandfonline.com/action/journalInformation?journalCode=ierv20

36. MODULE 5 – National immunization programmes (NIP) - WHO Vaccine Safety Basics [Internet]. [cited 2021 May 10]. Available from: https://vaccine-safety-training.org/national-immunization-programmes.html

37. Principles and considerations for adding a vaccine to a national immunization programme: from decision to implementation and monitoring. 2014 [cited 2021 May 10]; Available from: http://www.who.int/immunization/documents

38. Lu CY, Santosham M, An P Le, Kim A, Bravo L, Hadinegoro SR, et al. Survey of national immunization programs and vaccine coverage rates in Asia Pacific countries. Vaccine. 2012 Mar 16;30(13):2250–5.

39. สถาบันวัคซีนแห่งชาติ National Vaccine Institute, Thailand • วัคซีนพื้นฐาน [Internet]. [cited 2021 May 10]. Available from: http://nvi.go.th/index.php/vaccine-knowledge/epi-program

40. National Immunisation Program Schedule | Australian Government Department of Health [Internet]. [cited 2021 May 10]. Available from: https://www.health.gov.au/health-topics/immunisation/immunisation-throughout-life/national-immunisation-program-schedule

41. National Immunization Program for children | Policy&Services : KDCA [Internet]. [cited 2021 May 10]. Available from: http://www.kdca.go.kr/contents.es?mid=a30333000000

42. National Immunisation Registry [Internet]. [cited 2021 May 10]. Available from: https://www.nir.hpb.gov.sg/nirp/eservices/immunisationSchedule

43. Immunisation | NHM [Internet]. [cited 2021 May 10]. Available from: http://www.nrhmhp.gov.in/content/immunisation

44. Hexavalent, pneumococcal vaccine update included in national immunisation schedule | Latest news for Doctors, Nurses and Pharmacists | Infectious Diseases [Internet]. [cited 2021 Jun 2]. Available from: https://specialty.mims.com/topic/hexavalent--pneumococcal-vaccine-update-included-in-national-immunisation-schedule

45. Economic and physical diversity in Asia - Development - KS3 Geography Revision - BBC Bitesize [Internet]. [cited 2021 May 10]. Available from: https://www.bbc.co.uk/bitesize/guides/zvp39j6/revision/5

46. WHO | GAVI – The Global Alliance for Vaccines and Immunizations. WHO. 2010;

47. WHO | Key Facts about the WHO Prequalification Project. WHO. 2010;

48. History and Mission of WHO Prequalification | WHO - Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control) [Internet]. [cited 2021 Apr 11]. Available from: https://extranet.who.int/pqweb/about

49. WHO | Vaccine PQ. WHO [Internet]. 2020 [cited 2021 Apr 11]; Available from: http://www.who.int/immunization_standards/vaccine_quality/vq_index/en/

50. List of Prequalified Vaccines | WHO - Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control) [Internet]. [cited 2021 Apr 11]. Available from: https://extranet.who.int/pqweb/vaccines/list-prequalified-vaccines

51. Ahonkhai V, Martins SF, Portet A, Lumpkin M, Hartman D. Speeding access to vaccines and medicines in low- and middle-income countries: A case for change and a framework for optimized product market authorization. PLoS One [Internet]. 2016 Nov 1 [cited 2020 Oct 14];11(11). Available from: /pmc/articles/PMC5112794/?report=abstract

52. Dellepiane N, Wood D. Twenty-five years of the WHO vaccines prequalification programme (1987-2012): Lessons learned and future perspectives [Internet]. Vol. 33, Vaccine. Elsevier Ltd; 2015 [cited 2020 Dec 14]. p. 52–61. Available from: /pmc/articles/PMC5355375/?report=abstract

53. WHO | List of Stringent Regulatory Authorities (SRAs). WHO [Internet]. 2020 [cited 2020 Dec 20]; Available from: http://www.who.int/medicines/regulation/sras/en/

54. Jadhav S, Datla M, Kreeftenberg H, Hendriks J. The Developing Countries Vaccine Manufacturers' Network (DCVMN) is a critical constituency to ensure access to vaccines in developing countries. Vaccine [Internet]. 2008 Mar 20 [cited 2021 Apr

11];26(13):1611–5. Available from: https://pubmed.ncbi.nlm.nih.gov/18294742/

55. Poeloengan T, Raw I, Herrera Martinez L, El-Abbadi M. Meeting report Developing Country Vaccine Manufacturers Network (DCVMN), 26-27 April 2001, Bandung, Indonesia [Internet]. Vol. 20, Vaccine. 2002 [cited 2021 Apr 11]. Available from: http://www.vaccinealliance.

56. Pagliusi S, Leite LCC, Datla M, Makhoana M, Gao Y, Suhardono M, et al. Developing countries vaccine manufacturers network: Doing good by making high-quality vaccines affordable for all. Vol. 31, Vaccine. 2013.

57. Drug Lag, by Daniel Henninger: The Concise Encyclopedia of Economics | Library of Economics and Liberty [Internet]. [cited 2021 Apr 11]. Available from: https://www.econlib.org/library/Enc1/DrugLag.html

58. Wileman H, Mishra A. Drug lag and key regulatory barriers in the emerging markets. Perspect Clin Res [Internet]. 2010 Apr [cited 2020 Jul 22];1(2):51–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21829782

59. Andersson F. The drug lag issue: The debate seen from an international perspective [Internet]. Vol. 22, International Journal of Health Services. SAGE PublicationsSage CA: Los Angeles, CA; 1992 [cited 2021 Apr 11]. p. 53–72. Available from: http://journals.sagepub.com/doi/10.2190/9Y32-X86Y-M3F0-JQFC

60. Kataria B, Pandya A, Panchasara A, Panchal P, Parmar M. Drug lag for antineoplastic and immunomodulating agent approvals in India compared with the

US and EU approvals. Int J Basic Clin Pharmacol [Internet]. 2016 Dec 28 [cited 2020 Oct 11];5(2):335–40. Available from: www.ijbcp.com

61. Okabayashi S, Kobayashi T, Hibi T. Drug Lag for Inflammatory Bowel Disease Treatments in the East and West. Inflamm Intest Dis. 2018;3(1):25–31.
62. Vaccines Licensed for Use in the United States | FDA [Internet]. [cited 2021 Apr 11]. Available from: https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states
63. European Medicines Agency | [Internet]. [cited 2021 Apr 11]. Available from: https://www.ema.europa.eu/en
64. TGA Search -- [Internet]. [cited 2021 Apr 11]. Available from: https://tga-search.clients.funnelback.com/s/search.html?query=&collection=tga-artg
65. Vaccines [Internet]. [cited 2021 Apr 11]. Available from: https://cdsco.gov.in/opencms/opencms/en/biologicals/Vaccines/
66. 의약품안전나라 > 통합검색 > 의약품등 정보검색 [Internet]. [cited 2021 Apr 11]. Available from: https://nedrug.mfds.go.kr/searchDrug
67. ระบบตรวจสอบการอนุญาต [Internet]. [cited 2020 Feb 10]. Available from: https://porta.fda.moph.go.th/FDA_SEARCH_ALL/MAIN/SEARCH_CENTER_MAIN.aspx
68. Listing of Registered Therapeutic Products-Data.gov.sg [Internet]. [cited 2020 Oct 14]. Available from: https://data.gov.sg/dataset/listing-of-registered-therapeutic-products

69. National Pharmaceutical Regulatory Agency (NPRA) - Home [Internet]. [cited 2021 Apr 11]. Available from: https://www.npra.gov.my/index.php/en/

70. Global Vaccine Market Report Overview of MI4A [Internet]. 2018 [cited 2021 Apr 11]. Available from: http://who.int/immunization/MI4A

71. Maniadakis N, Kourlaba G, Shen J, Holtorf A. Comprehensive taxonomy and worldwide trends in pharmaceutical policies in relation to country income status. BMC Health Serv Res [Internet]. 2017 May 25 [cited 2021 May 10];17(1):1–17. Available from: https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-017-2304-2

72. Sumriddetchkajorn K, Shimazaki K, Ono T, Kusaba T, Sato K, Kobayashi N. Universal health coverage and primary care, Thailand. Bull World Health Organ [Internet]. 2019 Jun 1 [cited 2021 May 10];97(6):415–22. Available from: http://www.who.int/bulletin/volumes/97/6/18-223693/en/

73. Selecting Viruses for the Seasonal Influenza Vaccine | CDC [Internet]. [cited 2021 May 10]. Available from: https://www.cdc.gov/flu/prevent/vaccine-selection.htm

74. (Biological Products) Regulation on Approval and Review of Biological Products [Internet]. [cited 2021 Apr 20]. Available from: https://www.mfds.go.kr/eng/brd/m_27/view.do?seq=71480&srchFr=&srchTo=&srchWord=&srchTp=&itm_seq_1=0&itm_seq_2=0&multi_itm_seq=0&company_cd=&company_nm=&page=1

75. Ramamoorthy A, Pacanowski MA, Bull J, Zhang L. Racial/ethnic differences in

drug disposition and response: Review of recently approved drugs [Internet]. Vol. 97, Clinical Pharmacology and Therapeutics. Nature Publishing Group; 2015 [cited 2021 Apr 28]. p. 263–73. Available from: https://pubmed.ncbi.nlm.nih.gov/25669658/

76. Chee DH. Korean clinical trials: Its current status, future prospects, and enabling environment [Internet]. Vol. 27, Translational and Clinical Pharmacology. Korean Society Clinical Pharmacology and Therapeutics; 2019 [cited 2021 Apr 20]. p. 115–8. Available from: /pmc/articles/PMC7032966/

77. START WITH KOREA DISCLAIMER [Internet]. 2017 [cited 2021 Apr 28]. Available from: http://kcc.konect.or.kr/

78. Regulation of Vaccines in Malaysia – APNES [Internet]. [cited 2021 Apr 20]. Available from: https://enterovirus.nhri.org.tw/2017/11/17/regulation-of-vaccines-in-malaysia/

79. THERAPEUTIC PRODUCTS GUIDANCE GUIDANCE ON THERAPEUTIC PRODUCT REGISTRATION IN SINGAPORE Please visit HSA's Guidelines on Therapeutic Product Registration webpage for the latest updates. 2020.

80. WHO Expert Committee on Specifications for Pharmaceutical Preparations [Internet]. [cited 2020 Jan 29]. Available from: www.who.int/bookorders

81. Rashwan HH, Saat NZNM, Manan DNA. Knowledge, attitude and practice of malaysian medical and pharmacy students towards human papillomavirus vaccination. Asian Pacific J Cancer Prev. 2012;13(5):2279–83.

82. Chen L-K, Arai H, Chen L-Y, Chou M-Y, Djauzi S, Dong B, et al. Looking back to move forward: a twenty-year audit of herpes zoster in Asia-Pacific. BMC Infect Dis [Internet]. 2017 Dec 15 [cited 2021 May 20];17(1):213. Available from: http://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-017-2198-y