



# Understanding Public Vaccine Policymaking Through the Lens of Political Economy Analysis—Using Taiwan as an Example

## Citation

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Understanding Public Vaccine Policymaking Through the Lens of Political Economy

Analysis—Using Taiwan as an Example

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A Doctoral Thesis Submitted to the Faculty of

The Harvard T.H. Chan School of Public Health

in Partial Fulfillment of the Requirements

for the Degree of *Doctor of Public Health*

Harvard University

Boston, Massachusetts.

May 2020

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**Abstract**

Despite the epidemiological transition from the era of communicable disease to the era of non-communicable disease (the COVID-19 pandemic notwithstanding), dengue remains a growing threat to the public health of the world. Lack of effective treatment and scalable vector control measures justify the need for investments in the development of a dengue vaccine. The thesis documents an eight-month project with Takeda Vaccine Business Unit, using political economy analysis to understand public vaccine policymaking.

The field assignment experience consisted of four steps: the first step involved becoming familiar with the goals, functions, and culture of the host organization, Takeda Vaccines; this step was necessary in order to scope and adjust the focus of the deliverables appropriately. The second step focused on data collection, with Taiwan selected as the primary country for in-depth analysis of public vaccine policymaking. Several public vaccine introductions in the United States, Canada, Indonesia, and Malaysia were chosen from the literature to provide a broader context for comparison and analysis. The third step was to match the data collected on Kingdon's multiple stream framework to demonstrate the

usefulness of the framework in understanding the vaccine adoption processes. The fourth and final step, based on the aforementioned analysis, was to generate hypotheses that informed the development of a toolkit for Takeda's branch offices to prepare for the launch of a dengue vaccine in prioritized countries.

Although industry involvement in public vaccine policymaking has not been viewed as ethically appropriate by everyone, this project demonstrated that the industry plays an indispensable role in bringing a healthcare solution to a population in need. In this sense, the power of the market and its resources would be beneficial to public health. Technocrats and scientists involved in public vaccine policymaking explicitly adopt values of *objective utilitarianism*, while politicians adopt those of *liberal egalitarianism*; the combination of these two belief systems inform real-world decision-making. However, political considerations are able to trump the effects of different value principles and affect the final results of the policy decision, which would result in the decrease of transparency and consistency of the principles for vaccine policies.

Existing analytical frameworks of public vaccines fall short in explaining how public vaccine policies were introduced. The combination of political science, behavioral science, and lessons from environmental health can add value to the study of public vaccine policymaking, and health agenda setting.

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## **Acknowledgments**

I thank Tina for her constant support and sacrifices, my committee for its commitment in providing guidance, and my colleagues in Takeda for the receptive environment they created for me to learn and contribute.

## 1. Introduction

### 1.1. Dengue Infection

Dengue is a mosquito-borne infectious disease caused by the transmission of four dengue viruses (DENV) via two types of mosquitoes called *Aedes aegypti* and *Aedes albopictus*. There are four types of dengue viruses (DENV1, DENV2, DENV3, and DENV4) as classified by serotypes. DENV belongs to the genus *Flavivirus* in the family of *Flaviviridae*. The earliest record of dengue found to date was published during the Chin Dynasty (265 to 420 A.D.) in a Chinese encyclopedia of disease symptoms and remedies. It emerged as a global public health problem, after World War II, as a result of ecological disruption in Southeast Asia, global population growth, unplanned urbanization, lack of effective mosquito control, and the geographical expansion of *A aegypti* (Gubler, 1998). Amidst the global trend of declining communicable diseases, dengue stands out as countering that trend. The incidence of dengue has doubled every ten years in recent decades (Stanaway et al., 2016).

The transmission of the disease regularly occurs in at least 128 countries, putting almost 4 billion\* people at risk annually(Brady et al., 2012). The disease's clinical manifestations range from asymptomatic infection to life-threatening complications.

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\* Number of people living in areas at risk of dengue.

Asymptomatic infections, under-reporting of apparent cases, and limited lab capacity in endemic countries pose challenges in estimating the global incidence of dengue. The most commonly cited estimate of incidence for dengue infection is between 50 million to 100 million annually (Stanaway et al., 2016). According to Bhatt's model, around 10,000 deaths per year can be attributed to dengue. Africa and the Americas bear nearly equivalent burdens of dengue (16%, 14%, respectively), while more than 70% of the global burden is shouldered by Asia (Bhatt et al., 2013). Such distribution could be explained by the distribution of the primary vector *Aedes aegypti* (Kraemer et al., 2015). The burden of dengue on endemic countries places a strain on already overloaded healthcare systems and erodes economic growth, particularly in low and middle-income countries.

There is no effective antiviral treatment for dengue. The treatment remains supportive\* (WHO, 2009). An estimated 500,000 people are hospitalized due to severe dengue annually. The estimated case fatality rate is up to 2.5%, though it varies by country. The decline in case fatality rate over the years has been reported as a result of the improvement of case management, thanks to country-level capacity building supported by the World Health Organization (WHO, 2019a). The control and mitigation strategy is mainly vector control before an ideal vaccine is made available (WHO). The daily mean temperature

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\* "Supportive treatment" means treating the symptoms or complications associated with the disease, without being able to eliminate the pathogens.

and temperature variability are the two major predictors for dengue endemicity. Models predicted dengue's expansion to new geographical areas when climate change was considered. The localities predicted to be endemic for dengue in the future tend to have a less robust healthcare system (Ebi & Nealon, 2016). The burden resulting from the infection is so high that the WHO has listed dengue as one of the ten threats to global public health in 2019 (WHO, 2019c). Among the ten threats listed by the WHO, vaccine hesitancy is also related to dengue vaccine issues, which will be discussed further.

## 1.2. Vector of Dengue

Donald S. Shepard and colleagues assessed data from 141 countries and territories to estimate the economic burden of symptomatic dengue. It was stated that the total annual global cost of dengue illness was US\$8.9 billion (with a distribution of 12% fatal, 46% non-fatal admitted to hospitals, 34 non-fatal ambulatory, and 8% non-medical)\*. The figure surpassed that of other major infectious diseases, such as cholera and rotavirus gastroenteritis (Shepard, Undurraga, Halasa, & Stanaway, 2016). With the seemingly unabated intensity of dengue's global spread, this number will continue to grow and jeopardize the sustainability of other sectors, such as infrastructure or education. The current

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\* Ambulatory means outpatient care, non-medical referred to expenses incurred when patients seek remedies outside of the formal system. According to the same paper, the distribution of global dengue cases treatment is: 18% hospital, 48% ambulatory, and 34% non-medical.)

measures for mitigation of the dengue epidemic remain vector control, which includes: environmental management (e.g., cleaning containers that might be breeding sites for the mosquitoes), chemical control (e.g., spraying of insecticides), and personal protection (e.g., using repellants). However, it is difficult to maintain the effects of vector control using existing tools. After 15 years of low transmission of dengue under a successful vector control program in Singapore, the incidence of dengue reemerged. Eng-Eong Ooi and colleagues provided explanations of this reemergence, which included changing population immunity profiles and transmission patterns of the diseases(Ooi, Goh, & Gubler, 2006). In 2013, Partnership for Dengue Control (PDC) convened a meeting of international experts to assess the vector control tools for dengue prevention. The experts concluded that there was a lack of studies that provided evidence for positive health impact from conventional vector control methods. Since then, the new techniques that are under development fail to offer ways of scaling-up the small-scale successes to mega-cities, thereby impacting the population's health as a whole. These difficulties in using vector control as the sole solution to decrease the dengue transmission called attention to the necessity of a dengue vaccine as a complementary method to vector controls. “There is growing consensus among dengue experts that eliminating dengue as a public health burden can only be achieved by integrating vector control with vaccines.” (Achee et al., 2015).

### 1.3. Dengue Vaccine Challenges

The development of dengue vaccine dates back to 1929, where researchers advocated the use of phenol or formalin for the inactivation of dengue virus (Simmons, St. John, & Reynolds, 1931) (Blanc, 1930). What makes the development of dengue vaccine different and challenging is that patients with second dengue infection, of a different serotype than the first infection, bear an increased risk of severe dengue. Therefore, a vaccine that protects against all four subtypes is essential. The explanation of this phenomenon was first presented by Dr. Scott B. Halstead more than 30 years ago (Halstead, 1988). Halstead proposed that for an individual who had acquired immunity against one type of dengue virus but was then exposed to a heterotypic dengue virus, the antibody against that first subtype of dengue virus would have a sub-optimal neutralizing capacity. The sub-neutralizing antibody would enhance the replication of the subsequent virus in mononuclear phagocyte lineage and lead to a cascade of reactions that would result in increased vascular permeability, plasma leakage, shock, and even death. Such a response is called antibody-dependent enhancement (ADE). Other mechanisms explaining the increased risk of severe dengue after secondary infection have been proposed, but the ADE theory proposed by Halstead remains the more widely accepted one.

The first dengue vaccine to be licensed was Sanofi's CYD-TDV (Dengvaxia) (WHO, 2018a). It was first licensed in Mexico in December 2015, and by 2019 roughly 20 countries had approved its use. FDA granted its approval in May 2019 (FDA, 2019). In 2016 the

Philippines launched a campaign using Dengvaxia to vaccinate approximately 800,000 children. The program was reported to cost \$69.5 million to the Philippine health department, which is about 3% of the total annual budget of the Department of Health of the Philippines\* (Reuters, 2019b).

In November 2017, Sanofi announced the results of an additional analysis that the company had done to investigate the effect of the vaccine on dengue naïve vaccine recipients at the time of receiving the first dose. The result was later published in the New England Journal of Medicine. Sridhar and colleagues (Sridhar et al., 2018) reported that, compared to unvaccinated seronegative trial participants (from the placebo arm), the vaccinated seronegative participants had a higher risk for severe dengue and hospitalization. Within one month of Sanofi's announcement, WHO published an interim recommendation (December 2017) to vaccinate individuals who are seropositive at baseline only(SAGE, 2018)\*. Through several deliberations within the SAGE working group, from December 2017 to March 2018, the revised recommendation was published in April 2018. Two main approaches were considered in order for the vaccine to be used in public programs:

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\* <https://www.doh.gov.ph/doh-budget>

\* Seropositive at baseline means that participant was tested positive to have antibody against dengue by the time he/she entered in the trial.

1. In high transmission settings, as defined by locations with seroprevalence >80% among nine-year-old children\*, CYD-TDV could be considered without pre-testing;
2. In low and moderate transmission settings, only persons with evidence of a past dengue infection could be vaccinated (WHO, 2018b).

The revised recommendations have created a quandary for the decision-makers who wish to use Dengvaxia to combat dengue. There are very few locations that have seroprevalence >80% among nine-year-old children. Screening everyone to check eligibility for the vaccine creates logistic barriers and increases the program cost. Furthermore, people who received false-negative results could be deprived of the chance for vaccination. Conversely, patients who received false-positive results would be exposed to a higher risk of severe dengue and hospitalization. The sensitivity and specificity of the test at the point-of-care are crucial to render optimal positive predictive value, given the level of the prevalence of dengue at the location where it is used (Rodríguez-Barraquer, Salje, & Cummings, 2019). To date, there is no such ideal test available in the market. Whether we should use the vaccine to save lives or withhold it due to the relatively fewer vaccine-related deaths, became

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\* The age indication of Dengvaxia approved by FDA was from 9 through 16 years of age. A vaccine is normally recommended to be administered prior to the age that has the highest incidence of disease, which is at the lower end of this range of indication for dengue.

an ethical debate. The issue was compared to the trolley problem in the studies of ethics(Rosenbaum, 2018)\*.

Another ongoing debate is whether Sanofi should work with government officials to go back and check on those who received Dengvaxia and ascertain who was seronegative as a baseline to warn them of the risk of future severe dengue. The working group came to the overall conclusion that “*CYD-TDV still has a potential public health role, in the absence of currently available alternative solutions to combat the expanding problem of the global dengue burden*”(SAGE, 2018).

As a result of the safety concerns, the Philippines permanently halted the sales and distribution of Dengvaxia, and the Department of Justice charged Sanofi and government officials with alleged collusion(Reuters, 2019b). The concerns affected the people’s trust in the government and in other vaccines as well. According to The Vaccine Confidence Project, that measured the impact of the crisis in the Philippines, the percentage of people who strongly agreed that the vaccines were safe dropped from 82% in 2015 to 21% in 2018; those people who strongly agreed that the vaccines were important dropped from 93% in 2015 to 32% in 2018(Larson, 2019). Such a drastic drop in vaccine confidence was believed to be

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\* A trolley problem is a classic case discussion for ethics. Imagine there is a trolley running on the railway about to hit a group of people who cannot move. You can pull the lever for the trolley to switch track to save these people, but the trolley will kill one person on the other track. Should you do nothing and let the group die, or pull the lever to kill one and save the group?

associated with the outbreak of measles in the Philippines in 2019, according to a WHO report(WHO, 2019b).

In Oct 2019, Sanofi appealed to President Duterte of the Philippines to change the ruling on the permanent revocation of the Certificate of Product of Dengvaxia. It was done in the wake of increased dengue cases in the country, which also affected the daughter of President Duterte. The appeal to President Duterte was believed to be motivated by two facts. First, in August 2019, Duterte stated that he was open to the resumption of the government's Dengvaxia vaccination program to avert a national dengue epidemic. Dengue had already claimed over 600 lives nationwide since January of 2019. Second, it was reported that Duterte's daughter received Dengvaxia and had a breakthrough infection of dengue, which made the President take a day's leave to render care (Star, 2019). Because the President's daughter fell ill after Duterte expressed his openness to the resumption of Dengvaxia program. It is not clear whether the President was discouraged from supporting because the vaccine failed to avoid her daughter's infection or the personal experience would increase his awareness of the disease and lead to his support?

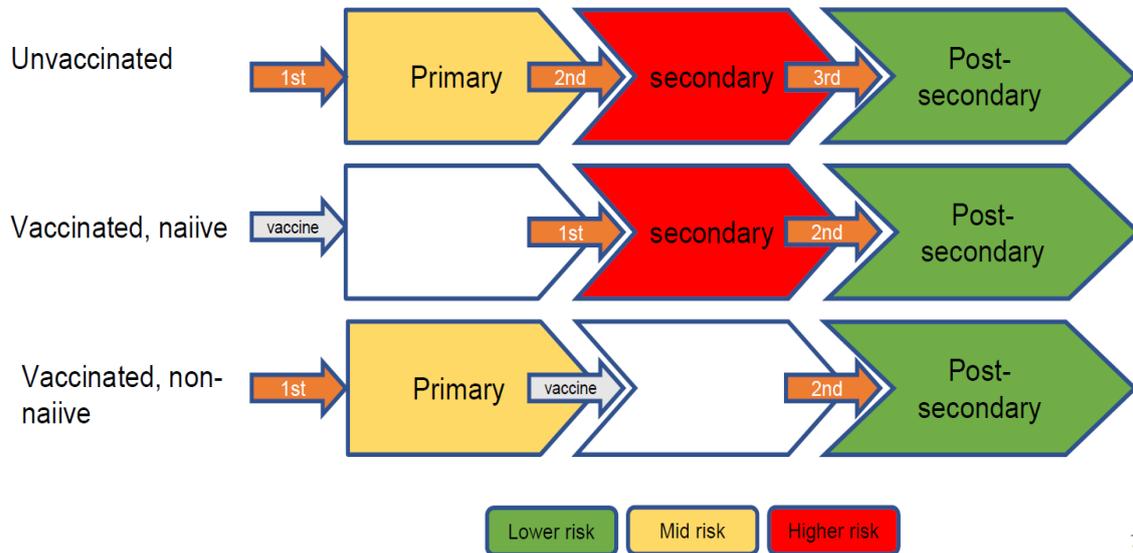
As of the time this thesis was written, the result of the appeal was still pending. It should also be noted that media involvement is relevant to our political economy analysis. This will be addressed in later chapters.

To understand why the dengue-naïve individuals experienced a higher risk for severe dengue and hospitalization after receiving Sanofi's Dengvaxia, scientists developed "the silent infection theory," based on Halstead's work (Refer to Figure (1)). It was believed that the dengue vaccine, when administered to the recipient, would act as a "silent infection." For those who were dengue naïve (the second row), when they encountered the first virus infection, the secondary-like reaction, which is ADE, would result in higher risk for dengue complications. For those who already contracted an infection for once at baseline, the immunization was considered a second infection. However, because the vaccine virus strain is an attenuated one\*, the risk was not elevated. The dengue vaccination helped the seropositive individuals at baseline skip the potentially more dangerous secondary infection and protected them against the consequences of the following infection (Flasche et al., 2016), (SAGE, 2018).

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\* Attenuated vaccine uses technology to decrease the virulent of the pathogen while keeping it alive.

**Figure 1: The Silent Infection Theory (modified from (Flasche et al., 2016))**



#### 1.4. Takeda - The Host Organization

Takeda Pharmaceuticals was founded in 1781 by Chobei Takeda I in Osaka, Japan, when he established a shop as a retailer of Japanese and Chinese herbal medicine. Mr.

Takeda was known for his customer-centric approach and integrity in business. His motto was “dealing with medicine as though the patients being treated were your children.”

Generations of his family successors upheld these values through written codes of honor. The

corporate philosophy of the company is referred to as "Takeda-ism" (Integrity, Fairness,

Honesty, and Perseverance). The first product that the company launched, that had broad

public health implications, was Panvitan, a multivitamin product, which served as a vital

nutrient supplement in war-struck Japan in the 1950s. In 1962, Takeda established its first

overseas in Taiwan, which handled manufacturing and marketing (Rodriguez, 2014).

The company launched one of its first blockbuster drugs, Lupron, for the treatment of prostate cancer in 1985, through the cooperation with Abbott Laboratories. Also, in 1985, Prevacid, a treatment for peptic ulcers, was launched. At around the same time, Takeda introduced Actos, an oral antidiabetic drug. These successful drugs established Takeda's presence in the international arena. The company expanded into North America and Europe throughout the 1990s and 2000s. In 2008, through the acquisition of Millennium Pharmaceuticals, based in Cambridge, MA, Takeda officially stepped into the world of oncology new drug research and development (Rodriguez, 2014). In January 2019, Takeda announced the completion of its acquisition of Shire, a \$62 billion deal, expanding its R&D capacities to cover the areas of oncology, gastroenterology, neuroscience, rare diseases, plasma-derived therapies and vaccines (Takeda, 2019). To date, it is one of the world's top 20 pharmaceutical companies by revenue, operating in around 80 countries. In 2018, Takeda was ranked 5th, after GSK, Novartis, Johnson & Johnson and Merck, among the world's major pharmaceutical companies (according to the "Access to Medicine Index"), thanks to its performance in improving the availability of medicines worldwide, based on the metrics of management, compliance, R&D, pricing, patients, capacity. and donation. (A. t. m. foundation, 2019). Takeda created the Vaccine Business Unit (VBU) in 2012 as an effort to globalize its existing vaccine business, which, at the time, was focusing on Japan's domestic vaccine market.

Takeda VBU's strategy to establish itself in this new market was through acquisition.

Takeda acquired LigoCyte in 2012, which developed a norovirus vaccine through VLP (virus-like particle) platform technology. Inviragen was acquired in 2013 for its pipeline assets, the vaccines for dengue and chikungunya. Dr. Rajeev Venkayya has been the president of VBU since its inception until the time this thesis was written (Rodriguez, 2014).

### 1.5. Project Overview

Lien was hired by Takeda through a third party as a contractor from August 5, 2019, to April 30, 2020. It was a full-time commitment. During this project period, he was based in Takeda's Cambridge, MA office, and joined the department of Immunization Science and Policy (ISP). The supervisor in the host organization was Vice President of ISP, Dr. Theodore Tsai, MD, MPH, FIDSA. Lien was tasked by Takeda Vaccine Business Unit to conduct political economy analysis to understand the processes through which a country would include a new vaccine in its National Immunization Programs (NIP). Based on the understanding gained from the analysis, a slide set of educational materials were created and incorporated in the toolkit provided for the branch offices for the preparation of the global launch of the dengue vaccine.

## 2. Analytical Platform

### 2.1. Literature Review

### 2.1.1. Takeda's Dengue Vaccine

Takeda's Vaccine Business Unit chose to prioritize dengue vaccine as the first market entry asset to the vaccine industry based on five criteria:

1. The dengue vaccine has the greatest expected impact on global public health.
2. The dengue vaccine has "commercial attractiveness."
3. The time the vaccine would likely take to be brought to market.
4. The competitive landscape for development of a dengue vaccine.
5. The probability of clinical success(Rodriguez, 2014).

The five criteria led to the decision to move the asset of dengue vaccine (acquired from Inviragen) forward. Takeda sought to be the second into the dengue vaccine market after Sanofi. With the rise of safety concerns of Dengvaxia in the Philippines and around the globe, Takeda VBU aspired to take the lead and make large scale public health impact through the introduction of its dengue vaccine. The candidate, TAK-003, also called TDV (tetravalent dengue vaccine), used live-attenuated DENV2 virus as a backbone, adding DENV1, DENV3, and DENV4 by recombinant technology\*. The vaccine was found to be safe, tolerated, and immunogenic\* in a schedule of two-doses, three months apart, in a phase

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\* A technology to join molecules of DNA or RNA from different species to make it into one.

\* Immunogenic means the vaccine was able to elicit immune response after being administered to the recipient.

I and phase II study(Sáez-Llorens et al., 2017), (Osorio et al., 2014). In September 2016, Takeda started its phase III, double-blinded, randomized, placebo-controlled trial to investigate the efficacy, safety, and immunogenicity of a tetravalent dengue vaccine (TDV) in healthy children aged 4 – 16 years old (ClinicalTrials.gov, 2016). Abbreviated as TIDES (Tetravalent Immunization against Dengue Efficacy Study), the study enrolled approximately 20,000 young children from dengue-endemic areas in Asia (Philippines, Thailand and Sri Lanka) and Latin America (Brazil, Colombia, Panama, Dominican Republic, and Nicaragua), where the unmet need for dengue prevention and control was high. In January of 2019, Takeda announced that the Takeda Dengue Vaccine (TDV) met the primary endpoint in phase III clinical trials (Rodriguez, 2014). On Nov 21, 2019, the seminal report of TDV's phase III (with 18 months of data) was published in the New England Journal of Medicine. TAK-003 was efficacious against symptomatic dengue in endemic countries. The overall vaccine efficacy against dengue infection was 80.9% (95%CI, 75.2-85.3), and the efficacy for protection against dengue related hospitalization was 95.4% (95% CI, 88.4-98.2). Unlike Dengvaxia's phase III study, TIDES recorded the baseline serostatus of the participants. This allowed the report to demonstrate the protection against dengue for those who were seronegative as a baseline, which was 74.9% (95%CI, 57.0-85.4) (Biswal et al., 2019).

Concerns over the sub-optimal efficacy against DENV3 among seronegative and wide confidence intervals for DENV4, due to low case number, were raised. Further interpretation

and readouts were expected to evolve as data beyond 18 months were collected and reported(Reuters, 2019a). Unlike existing vaccine companies, who often launched their products in developed countries before moving into low and middle-income countries, Takeda VBU plans to register and enter both markets simultaneously. This will mean that, along with the preparation of a regulatory dossier to be submitted to the FDA for vaccine approval, the company will also need to develop market strategies to enhance uptake in the National Immunization Programs for countries where dengue is endemic, i.e., countries in Southeast Asia and Latin America.

#### 2.1.2. Public-Funded Vaccine Policy

The Expanded Program on Immunization (EPI) was established by the World Health Organization (WHO) in 1974 to immunize infants against six diseases: diphtheria, tetanus, pertussis, poliomyelitis, tuberculosis, and measles(Kim-Farley, 1992) (Hyde et al., 2012). Aligning with the Declaration of Alma-Ata<sup>1\*</sup> in 1978 which called for commitments to achieve health for all, EPI was viewed as an important element of maternal and child health and primary health care. It was estimated that, in 2013, 111 million infants received vaccines for the protection against deadly diseases, which accounted for 84% of the world's children(Vakili, 2015). According to UNICEF, vaccines saved more than 2 million lives and

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\* The Declaration of Alma-Ata called for global stakeholders' commitments to achieving Health for All by the year 2000.

have transformed the global state of health and wellness (UNICEF, 2018). The majority of this achievement should be accredited to the public-funded vaccine programs that provided equal access to everyone. If run by a country, it is called the National Immunization Program (NIP).

Over time, NIPs have not only demonstrated the effects of decreasing maternal and child mortality but have also proved to be a prime mover in the development of healthcare infrastructures (Kim-Farley, 1992). Public-funded vaccine policy is not only a good investment for the government but also a great cost-saving strategy for the healthcare system in general. Empirical studies showed that the introduction of new vaccines reduced healthcare costs and had positive impacts on the healthcare system as a whole (Hyde et al., 2012). It was estimated that the return on investment from childhood immunization programs was 16 times greater than the cost of those immunizations in low and middle-income countries (Ozawa et al., 2016).

The economic benefits of vaccine programs are underestimated if the indirect benefits were not considered. This is because traditional vaccine impact studies focused only on saving on medical expenditure and health gain. Had the broader economic benefits for individual households and society as a whole were considered from the externality perspective, (i.e., psychological stress, childhood development, school attendance, and other macroeconomic indicators), the value proposition of vaccine programs would be even

stronger (Bärnighausen et al., 2014; Jit et al., 2015; Till, David, Elizabeth, & Jennifer Carroll, 2014).

Apart from economic angles, the public-funded vaccine program or the National Immunization Program could be used as a policy tool to prevent medical impoverishment and increase health equity (Verguet et al., 2013), (Loganathan, Ng, Lee, & Jit, 2016).

Modern technology has moved us forward from the era of the initiation of EPI. The invention and introduction of new and generally more expensive vaccines, including vaccines against hepatitis A, hepatitis B, *Haemophilus influenzae* type b disease, human papillomavirus infections, influenza, Japanese encephalitis, meningococcal meningitis, rotavirus, typhoid, zoster, and pneumococcal pneumonia, have made the decision of adopting a new vaccine in the public vaccine program a more complex one. This is because the prices of these new vaccines are much higher compared to the ones in the initial EPI, so the policymaking involves more prudent considerations for prioritization.

### 2.1.3. Vaccine Hesitancy

There is a broad range of factors that contribute to vaccine hesitancy, including the nature of the vaccine, the adverse health outcomes, lack of trust in the corporation, or in the public health agencies (Salmon, Dudley, Glanz, & Omer, 2015). The health communication strategy for immunization evolves with time according to the changing media environment

and the need of the public. Governments need to be more pro-active than in the past to promote immunization programs and avoid the detrimental consequences of vaccine hesitancy (Odone & Signorelli, 2017). When it comes to addressing vaccine hesitancy and issues around health communication, the literature is limited to the perspectives of the government or public health institutions; the perspectives from the industry have rarely been described in the literature. Furthermore, it is not enough to understand the vaccine hesitancy from a behavioral point of view. “Sometimes, the refusal of individual parents has a clear social or political aspect, such as local political strife or a social resistance movement. Under these conditions, in addition to vaccination cultures, an understanding of wide social and political processes is required to comprehend the prevailing gradations of acceptance” (Streefland, 1999). We will expand this discussion in the result statement section, based on the data collected.

#### 2.1.4. Dengue in Taiwan

Large scale outbreaks of dengue in Taiwan were recorded in 1915 and 1942. Similar to many other parts of the world, Taiwan experienced a period without large epidemics after World War II, until an outbreak of dengue hit an islet, Liu-Chiu, in 1981. 81.8% of the

surveyed population was infected (Hsieh et al., 1982)\*. This reemergence of dengue was believed to be the result of:

1. Fading herd immunity of the cohort that lived through the outbreaks before 1946.
2. The cessation of DDT spraying for malaria control in 1973.
3. Cancellation of the ban on traveling abroad in 1987.
4. Recruitment of foreign laborers, mainly from Southeast Asian countries, since 1989(W.-J. Chen, 2018).

Taiwan is located off the southeastern coast of mainland China in the western Pacific Ocean and has a tropical-subtropical climate that provides a suitable habitat for *Aedes aegypti* and *Aedes albopictus*, vectors of dengue. *Aedes aegypti* could only be found south of the Tropic of Cancer (23.5°N.), while *Aedes albopictus* could be found throughout the island. The distribution pattern of *Aedes aegypti* is believed to be due to the relatively lower winter temperature in the north(Tsai, Lin, Teng, & Yeh, 2018). Despite of the fact that there is a year-round presence of the dengue vectors, Taiwan is not considered endemic for dengue. According to the Taiwan Centers for Disease Control, dengue is thought to be introduced into the country annually through air travel from neighboring endemic countries. The epidemic

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\* Liu-Chiu's population was 15,558 in 1981

halts when the temperature drops in winter. This claim is supported by molecular epidemiology and phylogenetic analysis of dengue viruses from samples of imported cases. According to Huang and colleagues, 49.3% of the imported dengue cases were identified by infrared fever screening at airports between 2008 and 2010. Most cases arrived from Indonesia, Vietnam, Thailand, and the Philippines. The Philippines is the most frequent source. Other sources of importation include countries in the Indian subcontinent, the South Pacific region, and Latin America (J.-H. Huang et al., 2012). Although the north of Taiwan has a larger traveling population and receives more foreign workers, large outbreaks are limited to the south. In 2014, during a large outbreak, 15,732 cases of dengue fever were reported, with the vast majority of them (15,043 cases, or 96%) from Kaohsiung City, which is located in the more tropical southern region of Taiwan (Wang et al., 2016). A recent study showed that a land surface temperature of 13.8 °C was found to be the critical temperature for *Ae. aegypti* larvae, which results in the near disappearance of *Ae. aegypti* during winter in the subtropical regions of Taiwan (Tsai et al., 2018). Frontline dengue control officials know that when the flame of the epidemic of dengue in the south is inextinguishable, people pray for the cold front to come. It is believed that there is no overwintering of the dengue epidemic in Taiwan<sup>1\*</sup>. The geospatial distribution and the behaviors of the vectors determine the

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\* “No overwintering” means that the dengue viruses go extinct in Taiwan during the winter when the temperature drops below a cutoff value, the next epidemic that happens in the following year is newly introduced by importation, but not a result of the viruses staying around through the winter.

epidemic patterns in Taiwan. C-F Yang and colleagues hypothesized that the existence of *Ae. aegypti* is a prerequisite to the initiation of a dengue outbreak, while *Ae. albopictus* expands or maintains the scale of the outbreak (Yang, Hou, Chen, & Chen, 2014).

Dengue is a reportable infectious disease by law in Taiwan. Using the database from 1998 to 2017, Chen and colleagues demonstrated that 73,896 of 74,959 (98.62%) confirmed and reported cases were from Tainan City, Kaohsiung City, or Pingtung County in the southern part of Taiwan. With the central government being located in the north, the southern part of Taiwan is known to suffer from low economic development and investment. The inequality of economic strength, along with the skewed burden of dengue in Taiwan, has political implications, which will be further discussed in the result statement section.

#### 2.1.5. The Demographic Profile of Dengue Patients in Taiwan

The peak incidence of dengue infection, as well as that of dengue hemorrhagic fever (DHF), was initially known to happen largely among young children. A shift in the age profile has been documented in countries that are endemic to dengue. A study based on 45 years of data from the National Dengue Registry in Indonesia found that, for people aged above 15 years, DHF incidence increased and surpassed that of 5 to 14 year-olds since 1999 (Karyanti et al., 2014). A similar trend has been reported in various countries within Southeast Asia and Latin America (Cummings et al., 2009), (Ooi et al., 2006), (San Martín et

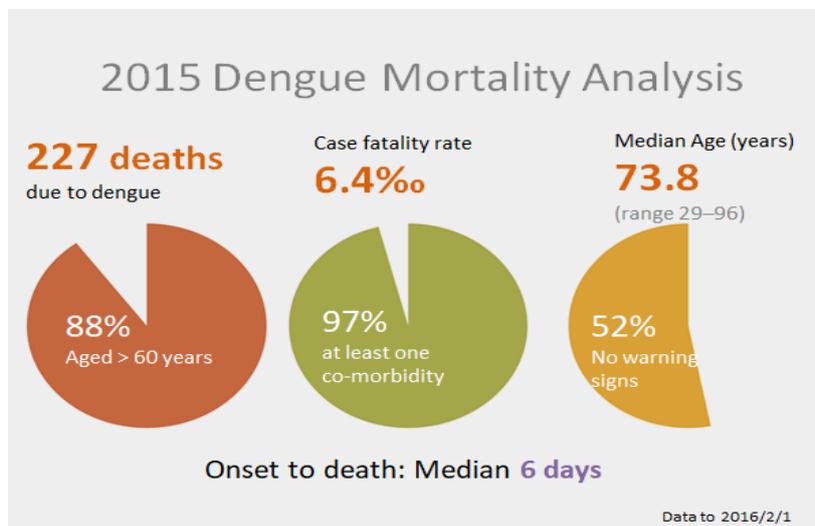
al., 2010). Cummings and colleagues proposed that the phenomenon could be explained by the shift in age structure due to lowering birth rate, decreased overall mortality, and its impact on the force of infection (Cummings et al., 2009). In an analysis published by the Taiwan CDC in 2015, Lo and colleagues tried to investigate the reason for the higher case-fatality rate (0.31%) of dengue during the outbreak in Tainan City in 2015, compared to that of Singapore in 2013, which was 0.04%. The median age for confirmed dengue in Tainan was 48 years old; those who were above 55-year-old comprised 40% of all cases, while in Singapore, the figure was 14%. The median age for mortality cases was 77 years-old in Tainan. The report estimated that 61% of the difference between the case-fatality rate between the two countries could be explained by age. The susceptibility to dengue infection among older adults in Tainan was higher compared to Singapore. The seroprevalence in Tainan for age above 55 was 36%; in Singapore it was 90% (Lo, 2015, in Chinese)<sup>1\*</sup>. The difference in seroprevalence in the two places could be explained by the fact that in Singapore, the annual epidemics exposed a large proportion of the population to dengue, resulting in the high seroprevalence in the older group accumulatively. In Taiwan, large outbreaks happened only every five to ten years, so older adults have lower seroprevalence. In the dengue epidemic of 2015, the death totaled at 228, among which 88% were > 60 years-

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\* The seroprevalence in Singapore is based on a report written by an official of TCDC who participated in an exchange program to visit Singapore's health department.

old, and 97% had at least one co-morbidity. The median age was 73.8 (29-96) (Figure 2). The fact that older adults had a higher risk of dengue mortality has several implications for the discussion of the thesis. First, the lethal cases being reported by the media could shape the perceived risk of dengue infection to the public. Second, being perceived as a disease of children or the elderly would have different political implications, which is an important element of political economy analysis. Third, the shift of epidemiology toward the senior population may have an implication on the implementation of a public vaccine program; for example, it might imply an aged-based catch-up recommendation on top of a routine recommendation.

**Figure 2: Mortality Analysis of Dengue by Taiwan CDC in 2015**



(Personal Communication with Taiwan CDC)

#### 2.1.6. The National Immunization Technical Advisory Groups (NITAGs)

With the introduction of various new vaccines, which tend to be more costly, the public vaccine decision-making became far more complex. It required more rigors, transparency, and consideration of different aspects in order to ensure that public health outcome is maximized under limited resources used for the national immunization programs (NIP).

According to Piso and colleagues, the decision to introduce new vaccines into NIPs should be unbiased, comprehensive, systematic, and based on deliberate, rational, comprehensible, and evidence-based criteria (Piso & Wild, 2009). To achieve this goal, ministries of health need to be equipped with relevant technical expertise from epidemiologists, health economists, modeling experts, vaccinologists, clinicians, as well as policy or legal experts to gather and review necessary evidence through clear processes in the establishment of a national immunization program. The majority of the industrialized countries, as well as some developing countries, have established technical advisory bodies to review proposed vaccines using agreed metrics to evaluate the justification of the inclusion of new vaccines. Such advisory bodies are normally referred to as National Immunization Technical Advisory Groups (NITAGs). In the U.S., Taiwan, and Korea, it is called the Advisory Committee on Immunization Practices (ACIP). In Singapore, it is called the Expert Committee on Immunization. For Canada, it is known as the National Advisory Committee on Immunization (NACI) (Plotkin, 2018). The development of NITAGs had been a priority for WHO. Working through its regional and country offices, WHO has been collaborating with

partners to build local capacities. Creating a culture to maintain the independence of experts, a clear approach in the case of conflict of interests, and a well-established evidence-based process are key elements and goals of such initiatives. At the same time, WHO also provides detailed guidance for the mode of operation of a NITAG, including the size, composition, nomination process, and even meeting frequency guidelines for countries that are working toward the aforementioned goals (Piso & Wild, 2009). According to WHO's guidelines, a NITAG is ideally an independent, expert advisory committee that is used as a technical resource supplying guidance to national policymakers and program managers to enable them to make evidence-based, immunization-related policy and program decisions (Cho, 2012).

#### 2.1.7. The NITAG of Taiwan

The NITAG of Taiwan carries the same name as that in the U.S., the Advisory Committee on Immunization Practices (ACIP). Taiwan's ACIP was established in February 1986. Before that time, the policymaking for the immunization program was based on informal consultation with experts in academic institutions in the country. The establishment of the Taiwan ACIP can be traced back to the outbreak of polio in 1982, during which 1,042 confirmed cases were recorded, leading to the deaths of 98 children. An investigation revealed that 65% of the population eligible for the polio vaccine did not receive the vaccine; only 6.5% finished the full schedule of three doses. In 1983, a school-entry mandate for the completion of immunization was implemented. An immunization record called "the Yellow

Card” needed to be presented to school nurses in order to enter elementary schools. The ACIP was established in 1986 due to the need of the country to make immunization policy in a timely and scientific way (Lee, 2002).

The number of members of ACIP in Taiwan is an odd number to avoid tied votes during disputes. There are 17 members for the year 2020. The members are subject matter experts who are nominated by the TCDC on a one-year non-remunerated contract. Although the ACIP was designed to incorporate experts from the disciplines of clinical medicine, epidemiology, and public health, the diversity was contingent on the willingness of the participation of experts. Pediatric infectious disease experts, by the nature of their training and backgrounds, are more involved in issues regarding vaccines. For example, in 2020, eleven out of the seventeen ACIP members are pediatricians, among which eight are pediatric infectious disease specialists. Out of the six experts who are not pediatricians, three are adult infectious disease specialists, one is a gynecologist, and one is an epidemiologist. In 2017, a geriatric medicine specialist was on the list, but the person did not participate in any meetings of ACIP, he did not receive the renewal of contract the following year. The different levels of experts’ participation imply that power and influence on public vaccine policies differ among members of the ACIP. Out of the 17 members, only one person lives and practices medicine south of the tropic of cancer, where the majority of dengue epidemics occur. This imbalanced representation had occurred through the years, between 2009-2019, the number of ACIP

members that live in the south and have first-hand experience in taking care of dengue patients was between zero to two. The difference in influence and in the experience of treating dengue patients will be elements being discussed in the political economy analysis (TCDC, 2019).

Taiwan CDC has long-lasting interaction with the US CDC. The first field epidemiology training program (FETP) in Taiwan was established through the help of the US CDC. The constant collaboration between the two parties was maintained through treaties and through TCDC sending staff to be trained as EIS (epidemiology intelligence service) officers in Atlanta. Despite the close exchange and the strong influence of the US system with Taiwan, the financial arrangement and the decision-making process for public vaccines in Taiwan were designed in very different ways.

For the US ACIP, once a vaccine recommendation is made, the funding decision through Vaccines for Children (VFC) requires another vote by the ACIP immediately afterward. Though a separate vote is required, the vote is not preceded by any discussion, but rather a perfunctory vote. This implies that the deliberations of ACIP's recommendation automatically considered the financial aspect of the policy. In contrast to this, the recommendations of public vaccines made by ACIP in Taiwan have no legally binding power for implementation. The recommended vaccines will be added to a list, according to the order of priority, and submitted to the Ministry of Health and Welfare. The list becomes part of a 5-

year strategic plan. The most recent strategic plan is called: “Plans to Replenish the National Vaccine Fund and to Promote Citizen Immunity Phase 3”. The phase 1 plan covered 2009 to 2013; the phase 2 covered 2014 to 2018; the current phase will be effective from 2019 to 2023. The National Vaccine Fund was established to fund the national immunization programs, with 35% of the funding coming from the governmental budget. The rest is from a fixed percentage of the total amount of tobacco tax collected. Therefore, the decision is out of the jurisdiction of the Ministry of Finance, providing the Ministry of Health and Welfare with a certain degree of autonomy. However, the trade-off is that the fund is limited; it does not change with the introduction of a new vaccine and could fluctuate with the sales of tobacco in the country. When extra funding is needed to support the inclusion of a new vaccine in the NIP, supports from the Executive Yuan (the Cabinet) and the Ministry of Finance are still needed.

Table (1) gives a comparison between the USACIP and TACIP. Apart from the financing mechanism, the key takeaway from this table is that TACIP uses consensus decision instead of majority rule to mediate disputes. Given the oriental cultural background, dissenters tend to suppress their own voices to keep the peace, which leaves room for influences other than the technocratic criteria of vaccines to come into play\*.

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\* The shortcoming of consensus decision compared to majority rule by vote is that the more outspoken members could direct the discussion and decision, making the power to influence the decision not equally distributed among members.

**Table 1: The Comparison between USACIP and TACIP**

	USACIP	NITAG of Taiwan (TACIP)
Analytical Framework	GRADE EtR (EtD)	HTA routinely done, no explicit analytical framework
Transparency of Deliberations	Live online video access to the public	Meeting minutes available to the public
Mechanism of Decision	Majority Rule	Consensus Decision most of the time
Timeline for Recommendation	Generally made within one year after registration	Registration does not trigger recommendation automatically
Categories of Recommendations	Recommend, not recommend, or decision-sharing	Recommendation or no recommendation
Impact on Private Market	Very few prescriptions after registration without recommendation	Private market activated since registration
Funding for Implementation	A perfunctory vote for Vaccines For Children (VFC) for children that are unable to pay. The recommendation will also trigger reimbursement by payers	Recommended vaccine will be on a wish list, which will be executed once the National Vaccine Fund is available or when a political decision was made.

### 2.1.8. NIP and the Funding Source

The NIP of Taiwan currently has ten vaccines that cover fifteen diseases (Hepatitis B vaccine, BCG vaccine, DTaP-Hib-IPV, PCV13, Varicella vaccine, MMR vaccine, Japanese encephalitis live chimeric vaccine, Influenza vaccine, Hepatitis A vaccine, and DTaP-IPV).

The vaccines that have been recommended and listed as a priority, but not implemented, are rotavirus vaccine, PCV for high-risk groups and older adults above 65 years old, and Hepatitis A vaccine for first-year high schoolers.

The reason for a vaccine to be recommended but not implemented is primarily based on the constraints of funding. In 2010, the National Vaccine Fund was established according to Section 27 of the Infectious Disease Control Law. The idea behind the fund is to allow earmarking, independently from fiscal performance, and rollover of the remaining fund to the next budgetary year. Using the year 2018 as an example, 73% of the National Vaccine Fund

(NVF) was from the tobacco tax, while 27% was budgeted by the central government. With the introduction and inclusion of new vaccines in the NIP, the annual expenditure of public vaccine grew ten times in a period of twenty years (1998-2018). The heavy reliance on tobacco tax for the public vaccine is problematic because the government's revenue from the tobacco tax fluctuates with time\*. Proposals to alleviate the burden of the NVF have been raised and debated. These proposals have included requiring a copayment for a vaccine, requesting reimbursement from the National Health Insurance Scheme, or promotion of corporate donations to the NVF. These proposals have yet to bring any change to the status quo. Given this constraint to include more new vaccines, the local governments have been adopting different public vaccine strategies to supplement what has been offered by the central government; they cherry-picked from the vaccines that had already made into the “wish list” for supplementary public vaccines. The beneficiaries of these vaccine policies are clearly defined and included: minors, older adults, low-or-middle income households, and the aboriginal ethnic group (Table 2). This is relevant to our political economy discussions in the later chapters\* .

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\* According to Taiwan CDC, The NVF received funds from tobacco tax: \$32.07M in 2016, \$92.7M in 2017, \$67.97M in 2018, \$55.97M in 2019, respectively.

\* The rest of the population will access the vaccine through out-of-pocket payments.

**Table 2: List of Public Vaccines Provided by Local Governments in Taiwan**

<b>City</b>	<b>Vaccine</b>	<b>People eligible</b>
New Taipei	Rotavirus vaccine	6-24 wks newborn from low-middle income households
Taichun City	Rotavirus vaccine	6-24 wks newborn from low-middle income households or from aboriginal ethnic families
Tainan City	Rotavirus vaccine	6-24 wks newborn from low-middle income households
Taipei City	Rotavirus vaccine	Subsidizing 6-32 wks newborn, eligibility by income
Chubei City	Rotavirus vaccine	Subsidizing newborns born after 1/1/2016 and parents residing for more than one year
Taichun City	PPV	1.60-74 y-o elderly 2.55-74 y-o aboriginal by ethnicity
Tainan City	PPV	65-74 y-o elderly
Taoyuan City	PPV	66-74 y-o elderly If received PCV13 at 65, can receive one dose of PPV23
Taoyuan City	PCV13	At the age of 65
Chiayi City	PPV	1.65-74 y-o elderly 2.50-64 y-o high risk group
Taipei City	PPV	1.65-74 y-o elderly 2.55 above aboriginal ethnicity
Chanhwa City	PPV	65-74 y-o elderly
New Taipei	PPV	65-74 y-o elderly
Hwalien	PPV	65-74 y-o elderly
Kin Men	PCV13	65-74 y-o elderly
Lien Chiang	PCV 13	65 above

### 2.1.9. Analytic Frameworks for Public Vaccine Policymaking

“Even if everyone agrees that healthcare resources have to be allocated and rationed, there is little agreement on the criteria that should be used for doing so.” (Roberts, 2008, p. 181). The situation described in this seminal book on healthcare system reform, published in 2008, evolved and improved over time, thanks to the initiative of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group. “GRADE, a systematic and explicit approach to making judgments about the quality of evidence and the strength of recommendations being presented (Atkins et al., 2004).”

To date, the tool for assessing evidence was adopted by more than 100 global organizations, including the WHO, the Cochrane Collaboration, and the National Institute for Health and Care Excellence (NICE) (Alonso-Coello et al., 2016). Based on the foundation laid by the GRADE initiative, the working group developed EtD (Evidence to Decision) through the project of DECIDE (Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence) (S Treweek et al., 2013; Shaun Treweek et al., 2013). The GRADE Evidence to Decision (EtD) framework was built to help decision-makers to move from appraising evidence to making decisions for clinical recommendations, health systems, or public health resource allocations (Alonso-Coello et al., 2016). EtD became a general framework based on evidence-based criteria to guide decision-making on intervention adoption (González-Lorenzo et al., 2015). Stemming from the need for transparent and science-based decision support for public vaccine programs, frameworks and tools were developed around the same period of time. González-Lorenzo and colleagues conducted a systemic literature review on existing frameworks for public vaccine decision-making and identified five systemic reviews and nine primary studies. The findings included:

1. Despite some differences in taxonomy, the EtD of GRADE and the frameworks identified by the review bear a large area of overlapping.
2. The most frequently used key criteria in the frameworks for determining the vaccine policy are the *burden of disease*, *vaccine characteristics*, *resource use*, and *feasibility*, while *values*, *preferences*, and *acceptability* were used less.

The Advisory Committee on Immunization Practices (ACIP) of the U.S. adopted the framework of EtD and called it EtR (Evidence to Recommendations) frameworks, to “ help panels making recommendations move from evidence to decisions, and to provide transparency around the impact of additional factors on deliberations when considering a recommendation” (ACIP, 2019). The six categories of criteria used by ACIP include *Problems, Benefits & Harms, Values, Acceptability, Resource Use, and Feasibility*. Except for the criteria of "*Feasibility*," each criterion requires specific scientific evidence or data for a judgment to be made.

Not all the analytical frameworks for public vaccine inclusion are products of the EtD of GRADE; some existed and evolved before the introduction of EtD. We wanted to look further to know if there were frameworks that encompassed different aspects of public vaccine considerations. Burchett and colleagues conducted a systemic review on the decision-making of adopting a new vaccine and found 26 articles presenting vaccine decision-making frameworks, 21 empirical ones for vaccine adoption, and 19 theoretical essays. The criteria used in the 21 frameworks in the report were classified into 9 categories: *the Importance of the Health Problem, Vaccine Characteristics, Programmatic Considerations, Acceptability, Accessibility, Equity and Ethics, Financial/Economic Issues, the Impact of Vaccination, Consideration of Alternative Interventions, Decision-Making Process*. (Burchett, Mounier-Jack, Griffiths, & Mills,

2012). Comparing this list with the EtR used by ACIP, *Accessibility, Equity, and Ethics* stand out, pertaining to the coverage for the targeted, or vulnerable groups in the population.

The analytical framework that has the largest number of criteria is used in Canada. In response to the increase of divergence of provincial and territorial immunization programs, Erickson and colleagues built a framework by analyzing information collected from 23 key experts and officials involved in the decision-making of local vaccine programs across the country. The framework includes 58 criteria, classified into 13 categories, including *the Burden of Disease, Vaccine Characteristics and Immunization Strategy, Cost-Effectiveness, Acceptability, Feasibility, and Evaluability of Program, Research Questions, Equity, Ethical, Legal and Political Consideration* (Erickson, De Wals, & Farand, 2005). This tool has been used systemically since 2005 by Canada's NACI (National Advisory Committee on Immunization), and provincial technical advisory committees (De Wals, Espinoza-Moya, & Béland, 2019).

These frameworks bear similarities, except for differences in wording and slightly different definitions of terms used. The table (3) and (4) listed the criteria that are common or different across different frameworks for comparison (ACIP, 2019; H. Burchett et al., 2012; H. E. D. Burchett et al., 2012; Erickson et al., 2005)

**Table 3: Common Criteria for Different Vaccine Frameworks**

Frameworks	Common Criteria				
US ACIP	Problem	Benefits & Harms	Acceptability	Resource Use	Feasibility
Canada	Burden of disease	Vaccine characteristics, cost-effectiveness	Acceptability		Feasibility, Immunization Strategy
Review of 21 frameworks	The importance of health problem	Vaccine characteristics, impact of vaccination	Acceptability	Financial, economic issues	Programmatic considerations
Review of 7 GAVI eligible countries★	The importance of health problem	Vaccine characteristics, impact of vaccination	Acceptability	Financial, economic issues	Feasibility, programmatic considerations

(ACIP, 2019; Burchett et al., 2012; Erickson et al., 2005)

★Bangladesh, Cameroon, Ethiopia, Guatemala, Kenya, Mali and South Africa

**Table 4: Unique Criteria to Different Vaccine Frameworks**

Frameworks	Unique Criteria
US ACIP	Values
Canada	Evaluability of the program, Equity, Ethical, and Political Considerations★
Review of 21 frameworks	Equity, Ethics, and Consideration of alternative interventions
Review of 7 GAVI eligible countries	Decisions made by neighboring countries

(ACIP, 2019; Burchett et al., 2012; Erickson et al., 2005)

★Limited to whether the decision will generate controversy, or whether it will produce immediate political benefit or risk

To summarize, all the frameworks include common elements of:

1. Problem/burden of the disease
2. Characteristic of the vaccine and its cost-effectiveness

3. Acceptability
4. Feasibility of implementation

ACIP's EtR includes "values" that are unique among other frameworks. The criterion of value was described as "does the target population feel that the desirable effects are large relative to undesirable effects?" The lack of "values" as a criterion in other frameworks, maybe due to the difficulty in estimating the value and preference of the targeted population.

Apart from the "evaluability of the program," Erickson's Canadian framework includes "political consideration," which is unique among other frameworks. However, in the application, the criterion only captures whether a vaccine program would arouse debate or cause political risks to the government that implements it.

In general, these analytical frameworks increased the transparency of decision-making by reporting the deliberations, the convergence, and the divergence of opinions of experts in a structured way. They helped with the priority setting of vaccines and even served as a tool for educating the health professionals and the public on immunization programs. However, there are limited publications that describe the real impact of these frameworks (Erickson et al., 2005). The limitations to the applications are as follows:

First, such tools do not provide guidance or practical details involved with the actual processes of vaccine adoption. There is no stipulation or specification on how to assess the vaccine based on certain criteria. For example: What is the best measure to use when evaluating the benefit and risk of a vaccine? Part of the reason is that these frameworks are generally qualitative in nature (González-Lorenzo et al., 2015).

Second, the frameworks are generally not used to evaluate competing priorities. Taking EtR of ACIP, for example, each vaccine is evaluated as a vertical program, leading to three results of the appraisal of the evidence: recommended, not recommended, or clinical decision (or shared decision). It is not designed to generate a composite score for comparing one vaccine over another. This is the reason why to understand why one vaccine is recommended while another is not required qualitative research. There is no quantitative output of the analytical frameworks for comparison.

Third, not every country's NITAG recommendation is tied to the implementation by law. The recommendations made by NITAG have significant impacts on the government's vaccine policy, but they are considered advice, not legally binding orders. The time between a recommendation was made to the implementation varies across countries(Blank, Schwenkglens, Sardos, Patris, & Szucs, 2013). The frameworks generally do not account for timelines of implementation, so they can't reflect urgency. In the 21 frameworks presented by Burchett's review, only one framework includes a time-sensitive criterion, which is "cues to action, e.g., disease outbreaks" (H. E. D. Burchett et al., 2012).

Fourth, the analytical framework is not an algorithm or a scoring system that quantifies the qualities of different vaccine options. This is why the ACIP members could not be replaced by artificial intelligence. Since the members are human beings, their decision making is arguably subject to factors not included in the analytical frameworks, which justifies the need for a political economy analysis to decipher the decision-making processes.

From the industry point of view, to use these frameworks to inform actionable plans of market access strategy becomes a matter of checking the boxes of these criteria and sponsoring studies to generate evidence. For example, to gain a better score in the "*values*" criteria of EtR

used by ACIP, companies would sponsor a study that provides evidence on the target population's preference related to vaccination's benefits and risks. Apart from the list of items to check, the frameworks do not provide pathways.

#### 2.1.10. Political Economy Analysis

From the discussions of the previous section, technical considerations listed by the frameworks fall short in helping us understand how a new vaccine gets adopted in countries. To understand how and why a vaccine makes its way to NIP, it is critical to put the sociopolitical and other contextual factors in the picture (De Wals et al., 2019).

“Political economy analysis investigates the connection between wealth and power, politics and economics, nation-states, and markets” (Hoogvelt, 2001) (Bump & Reich, 2013). In recent decades, the political economy has gained popularity as a sub-field of economics. It helps to explain complex processes such as economic reform, the interaction of political institutions and economic outcomes, and corruption, all of which are both political and economic phenomena (Alesina, 2007). In this project, the political economy analysis serves as an approach to consider politics and economics in the distribution of resources. The literature has very limited amounts of publications that used political economy analysis to describe how a vaccine gets included in the National Immunization Program.

#### 2.1.11. Kingdon's Multiple Streams Framework

In 1984, Professor John W. Kingdon from the University of Michigan published a book: *Agendas, Alternatives, and Public Policies* to propose a public agenda-setting framework in the area of political science (John W. Kingdon, 1984). The framework has become one of the most

cited works in the studies of agenda-setting and public policy\*. The work derived from qualitative interviews with decision-makers in three policy issues in the U.S.: *healthcare reform*, *transportation deregulation*, and *waterway user fees*. In his classic book, Kingdon proposed to use three streams to understand how a policy gained attention and was made into the government's agenda: the problem stream, the policy stream, and the politics stream. We will refer to this framework as Kingdon's MSF (multiple stream framework) in the following discussions. According to MSF, *the problem stream* tries to address the question: "What makes people in and around the government attend, at any given time, to some subjects and not others?" (Béland, 2016). In other words, the issue needs to be perceived as a burden that should and can be addressed. *The policy stream* is described as "where a set of solutions or policies are proposed to address the problem". *The politics stream* is defined as "where the political environment creates a window of opportunity to produce change." Kingdon theorized that the convergence of the three streams would create a limited period when the policy change is possible, which is called "policy window." It takes the "*policy entrepreneurs*": individuals or groups of people who play the role of policy advocates and serve as a bridge between the technocrats and bureaucrats to seize the opportunity of "policy window" for policy reform to take place. Ten years after the first book's publication, Kingdon published two lesser-known chapters that theorized the formation of policy ideas, which contribute to the ideational approach in the studies of public policy (Béland, 2016; J. Kingdon, 1994; John W Kingdon, 1993)\*.

MSF originated from the domestic policy environments of the U.S. The framework was not only used extensively in the analysis of health policy reforms but also in the global health agenda

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\* As of the time this thesis is written, there are more than 23,000 scholarly citation according to google scholar.

\* In these later works, Kingdon described that ideas float around in a so-called "policy primeval soup" and evolved by colliding and combining with other ideas. Since policy ideas and options about the solution for vaccine-preventable diseases are more succinct and, sometimes, with fewer options, we will only adopt the work published in 1984 as the framework for analysis in this thesis.

arena. Reich modified Kingdon's political stream into five sub-streams to explain why the international health aids agenda favors child health over adult health (Reich, 1995)\*. The five sub-streams under the political stream are:

1. ***Organizational politics stream***: “Efforts by organizations to use their resources and power in seeking to control issues and decisions so that the outcome will support and enhance their own position.” The colloquial version of the explanation is: “Where you stand depends on where you sit.” Although organizations would still use technical, rational analysis to support their stands, the goals are to maintain the very existence and influence the organization has. Applying the stream to the dengue vaccine scenario, we would want to know if a vector-control institute in a country resists the idea of a dengue vaccine in order to maintain its position in the combat to dengue.
2. ***Symbolic politics stream***: “Capacity of individuals and organizations to use images and languages as symbols that can create and quell issues, to arouse and satisfy particular constituencies or mass publics.”
3. ***Economic politic stream***: “The ability of private for-profit organizations to shape the boundaries of an issue and to give greater priority to one issue over others.”
4. ***Scientific politics stream***: “Recognizing the study of public health problems is shaped by the sources of financial support, such studies can generate new ideas for the agenda and confer legitimacy on one idea over others.”
5. ***Politician's politics stream***: “Politicians make choices based on their sense of what is both feasible and beneficial. The above four streams combine to affect the calculus of

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\* Professor Michael R. Reich from Harvard School of Public Health.

‘political feasibility’ used by national politicians to determine whether a problem achieves a high place on the country’s policy agenda.”

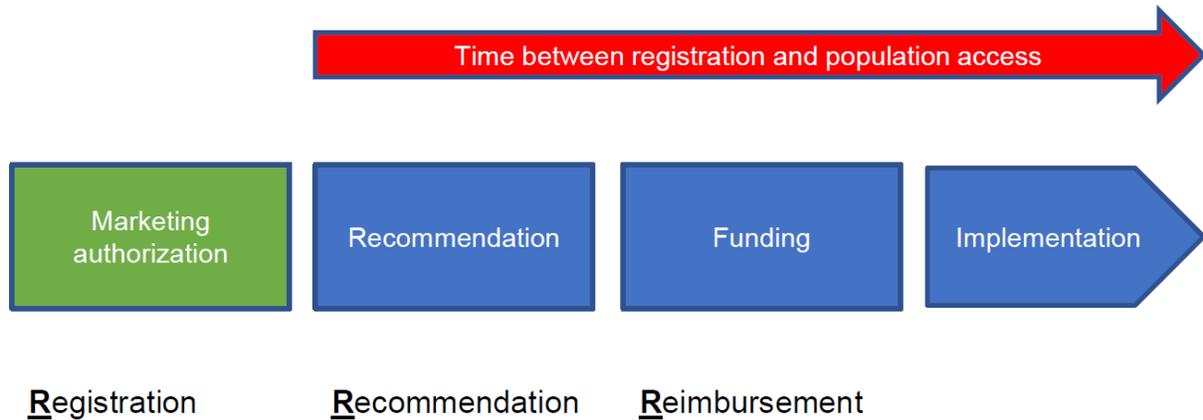
These five sub-streams under the politics stream have proven extremely helpful with the analysis of the public vaccine policy, which does not exist in the literature (according to recent search). We will come back to these five streams in the result statement section.

While there are abundant articles regarding MSF’s application to health policy agenda-setting, there are very few that deal with the public vaccine policy.

## 2.2. The Problem

Access to the vaccine is expected to be at the population level to maximize the impact on public health. After a vaccine is licensed, individuals have access to the protection through the market, in most cases, via out-of-pocket channels. It is only when the vaccine is recommended by the advisory experts and funded by a national program that the government could further implement the policy and work toward providing the vaccine to the population. The process was illustrated by P.R. Blank and colleagues: “from marketing authorization to recommendation to funding to implementation” (Blank et al., 2013). Another way to depict this process is the 3 Rs of vaccine access: Registration, Recommendation, and Reimbursement (Figure 3).

**Figure 3: From Registration to Access (modified from (Blank et al., 2013))**



A study coordinated by the European Vaccine Manufacturers Group (EVM) looked into the access time (defined by the time between registration to >50% of the indicated population has access) of three vaccines (HPV vaccine, rotavirus vaccine, and pneumococcal conjugate vaccine (PCV)) in 17 European countries revealed that the median access time was 6.4 years. The time for the development of a positive vaccine recommendation took up more than 90% of the entire access time (Blank et al., 2013). Access time in other parts of the world could take even longer. The low and middle-income countries gained population access to the Hepatitis B vaccine and *Haemophilus influenzae* type b (Hib) vaccine around two decades later than the industrialized countries (Chokshi & Kesselheim, 2008). This delay created more disease burden and a negative impact on public health over the time that would otherwise have been prevented by the appropriate vaccines. In the industry terms, the delay in recouping from the investment in the vaccine prevents companies from investing in research and development to meet more unmet medical needs.

The vaccine adoption decision is complex and idiosyncratic. The metrics applied by each country are different. There is a paucity of advice in the literature on what factors could expedite

or prolong the process. Studies that take into account the socio-cultural, economic, and political context of the decision-making process are even more scarce.

### 2.3. The Research Question and Assumptions

The research questions:

1. What are the socio-cultural, economic, and political contexts of the adoption of new public vaccines (using Taiwan as an example)?
2. How can we use this information to inform strategies for a pharmaceutical company to introduce its new dengue vaccine to a targeted country?

The assumptions:

1. Kingdon's Multiple Stream Framework could be applied to help understand the process of vaccine recommendation.
2. Political thinking and considerations permeate the processes of public vaccine introduction more than described by the analytic frameworks.
3. Gaining the knowledge of the different streams of vaccine agenda setting would provide the branch offices of the company an extra tool to develop a strategy for the dengue vaccine's market access.

### 2.4. Methods

**The Primary Data Source:** The primary data of our political economy analysis came from qualitative interviews of key informants from Taiwan. The key informants were high-level stakeholders or key opinion leaders (KOLs) from government, academia, NGOs/civil society, and the private sector. The key informants were identified through the below sources:

1. Literature review related to the public vaccine in Taiwan to identify key individuals and institutions.
2. Snowballing sampling. Respondents were asked to recommend potential participants in the interview. It was envisioned to identify around twenty-five potential candidates. The breakdown of respondents was expected to be: seven national-level government officials, four from academic institutions, three from NGOs/civil society, two providers.

Purposive sampling was done to secure the relevant, critical stakeholders related to the public vaccine and/or dengue control affairs. These people were selected based on their depth of knowledge in the domain and their experience in the fields related to the dengue control or vaccine program. Given that there were so few experts in the country that had participated in the process of vaccine policymaking, the selection of interviewees could be described as being comparable to that of an elite interview (Richards, 1996).

The participants were provided with a set of semi-structured questions before the interview via emails. The questions differed according to the distinct role and expertise of the interviewees. A 60 minute, in-person interview was conducted individually by the author; the average time for the interview was 65 minutes. The interviews took place between October and November of 2019 in Taiwan. This approach resulted in N=1 for certain categories of participants. The intention was not to infer that the data collected from such individuals would represent the opinions of his/her category but to treat the interview as part of a meaningful data set that might help the construct of the hypotheses. The qualitative analysis was based on thematic analysis. The code generation process was a mixture of being inductive and deductive. The deductive approach was the overlaying of the codes to stakeholder mapping and Kingdon's MSF. The inductive approach was used to allow the finding of unexpected nuances, particularly

when a code could not be overlaid to the pre-decided Kingdon's framework. Appendix 5.6 listed the questions that are unique to the specific categories of the interviewee. Depending on the time spent on different questions, the amount of information gathered varied.

**The Secondary Data Sources:** Government policy documents, annual reports from the Ministry of Health, grey literature, newspaper articles, YouTube videos of speeches given by experts or government officials, and reports related to dengue or public vaccine policy are collected and reviewed for expansion of the scope of the data.

**Verification of Primary Data:** The primary data was compared to the secondary data for verification and triangulation.

Appendix 5.6 shows that questions for different categories of interviewees differed.

Examples included:

- ACIP member: Can you recall any instance when there was a dispute among the experts? How did you resolve it?
- Director-General of the local departments of health: Do you have your own ACIP? How was the public vaccine decision made at your level?
- Journalists: What are the factors that would affect the decisions to cover an outbreak in the news?
- Anti-vaccine association: Describe the focus and the goal of your organization. How do you describe the impact of your organization on the public vaccine policy?
- Clinicians: Please talk about your experience of the implementation of the public vaccine policy in Taiwan.

Based on the data collected from the qualitative interviews and literature reviews, the results were structured following the steps below:

1. Conduct a stakeholder mapping that describes the key stakeholders that would affect the public vaccine policy in Taiwan using the framework of interest, positions, and power (Lucy Gilson et al., 2012; Roberts, 2008).
2. Describe the cases of different vaccines that were adopted in Taiwan's NIP and the cases of Indonesia, Canada, the U.S. and Malaysia (Appendix 5.1-5.4) through the lens of political economy.
3. Aggregate data from the case points from Taiwan, Indonesia, Canada, the U.S., and Malaysia and overlay them onto Kingdon's MSF to examine the ability of the framework to explain the processes of public vaccine adoption.
4. Develop an essential question list based on findings from the above exercises to help Takeda's branch offices approach vaccine recommendations in the local context.

### **3. Results Statement**

#### **3.1. The Data**

Table (5) sorts the interviewees by the categories of their profession. The former Minister of Health was put in the category of the ACIP but not among the Ministry of Health Officials. This is because the questions directed at this individual were focused on his role as a current ACIP member, as opposed to his role as a Minister in the Ministry of Health. One out of twenty-four people requested (4.16%) did not respond to my request for an interview. The person is one of the ACIP members who is not a physician but an expert in vaccine cost-effectiveness. Because

all the ACIP members interviewed were clinicians, missing this interviewee might compromise the perspectives of public health, particularly the ones from cost-effectiveness.

**Table 5: List of Interviewees by Profession**

<b>Professions</b>	<b>Note</b>	<b>Number (% of total interviewees)</b>
ACIP members	1 current chair, 1 former chair, and 1 former Minister of Health	5 (22%)
Journalists	20+ years of reporting health-related news	2 (9%)
Ministry of Health Officials	1 former DG of Taiwan Centers for Disease Control, 1 former DG of Health Promotion Bureau	4 (17%)
Anti-vaccine movement	1 president of NGO, and 1 scholar that studies the movement	2 (9%)
Medical Society	1 chair of Family Medicine Society	1(4%)
Clinician	3 pediatricians from community clinics	3(13%)
Vector Control Experts	2 scholars of entomology	2(9%)
Frontline Disease Control Workers	1 TCDC branch medical officer, 1 former employee of TCDC branch	2(9%)
Director-General of Local Department of Health	1 DG from non-endemic city, 1 DG from endemic city	2(9%)

**Data Analyzed:** 25 hours of audio recording was transcribed in Chinese using paid software.

Local publications, government publications, and grey literature were gathered extensively.

### 3.2. Stakeholders Mapping

This part of analysis was based on the methodology illustrated by Gilson (Lucy Gilson et al., 2012). We analyzed the stakeholder’s interests, positions, and power with regard to general public vaccine policy, as well as dengue vaccine policy, when applicable. The definitions of the three aspects of the metric were listed in Table (6). The metric was a simplified and combined version of the works of Roberts and Shmeer (L. Gilson et al., 2012; Roberts, 2008; Schmeer, 1999).

**Table 6: The Metrics for Stakeholders Interest, Positions, and Power**

Interest	The degree to which stakeholders likely to be affected by the policy change.
	The advantages and disadvantages that implementation of the policy may bring to a stakeholder or his/her organization.
Positions	Whether the stakeholder supports, opposes, or is neutral about the policy.
	Involves assessment of intensity of each group's position on an issue.
Power	The ability of the stakeholder to affect the implementation of the health reform policy
	The Judgement of the level of force with which the stakeholder might support or oppose the policy is based on the quantity of resources (human, financial, technological, political, and other) available to the stakeholder and its ability to mobilize them.

Based on the data collected from qualitative interviews and literature reviews, the stakeholders were mapped onto the forcefield mapping\* (Table 7) for the visualization of their power and position regarding the public vaccine policy.

**Table 7: The Forcefield Mapping for Vaccine Policy Stakeholders in Taiwan**

Power	High Support (+2)	(+1)	Medium (0)	(-1)	High Opposition (-2)
High	ACIP, Centers for Disease Control of MoHW,		Executive Yuan (Prime Minister's Office), media, legislators	Bureau of Health Promotion, Bureau of National Health Insurance, MoHW	
Medium		Member of councils of municipalities, Academic Medical Societies	Hospital managers, Leaders of vector control programs		Medical Profession Associations
Low	Frontline dengue control workers		Vector control companies	Anti-vaccine movement, primary care doctors	

- **ACIP:** The chairman of Taiwan’s ACIP has long been a strong advocate for immunization. Several members of the ACIP are actively involved in an NGO called Taiwan Immunization Vision and Strategy (TIVS). TIVS advocates for increasing

\* It is a two-dimensional table for positioning stakeholders according to their power and position with regard to a certain policy. Those on the left upper are the most powerful and supportive of the policy. Those on the right upper are the most powerful and least supportive, which are the biggest opponents.

vaccine coverage and accessibility for the general public. Members of ACIP would speak to the media under the requests of TCDC when uptakes of the seasonal influenza vaccine by the public are low. From the white paper on public vaccine policy that TIVS published (TIVS), one can see that the chairman of ACIP took a position to advocate for the budget of public vaccine to be increased. Although those who participate in TIVS do not represent the opinions of all other members, they are the leading coalition, or so-called “core, or active members” of ACIP. The core members advocate for broader inclusion of indirect costs to vaccine-preventable diseases (such as work-day loss, school absenteeism, and psychological burden) when it comes to calculating the cost-effectiveness of the vaccine. The ACIP made a prioritized list of vaccines to be included in the NIP. There is not a set timeline for the government to bring it to action. Some ACIP members have been outspoken in the public arena to push for the realization of these priorities. The position toward public vaccine is given: 2+, for “high support.” Further, given the authority to advise the vaccine policy, the power is defined as “high.”

- *“We know that rotavirus has very low mortality in the country thanks to the robustness of our healthcare system, but when you look at the troubles that the disease causes to the parents, it worth it. I mean, when you include the indirect costs, it will always be cost-effective.”*
- **TCDC:** TCDC is a governmental agency that is responsible for the control of infectious diseases in the country. Different from the USCDC, non-communicable diseases are under the jurisdiction of TCDC’s parallel organization, the Bureau of Health Promotion (Taiwan BHP or TBHP). Senior TCDC officials take pride in telling the stories of the “glorious war against chronic hepatitis B” when Taiwan was the first country in the

world to provide HepB vaccination for all newborns in the 80s (D.-S. Chen et al., 1987; K.-Y. Huang & Lin, 2000). Feeling obliged to continue the legacy of excellence in immunization related affairs, two former Director-Generals of TCDC worked proactively to push for Taiwan to have its own vaccine manufacturers. This initiative dated back to the outbreak of EV71 in 1998 in Taiwan, when 129,106 cases of hand-foot-mouth disease and 78 deaths were reported (T.-Y. Lin, Twu, Ho, Chang, & Lee, 2003). Along with seasonal influenza, enterovirus and dengue are still the three diseases that elicit the most media attention and public anxiety, therefore placing the highest pressure on disease control officials. In 2017, the TCDC convinced the Executive Yuan to utilize the “second preparatory fund,” a fund reserved for the government’s emergency response to procure 6 million doses of influenza vaccine to cover 25% of the whole population. It is safe to say that TCDC officials are unanimously firm believers of the benefits of vaccine for public health (high support 2+). TCDC officials could take initiatives to invite the industry to share the latest updates of developing vaccines in ACIP meetings (similar to the USACIP’s industry day), form working groups to gather evidence and assign tasks to conduct health technology assessment for a specific vaccine. The “power” assigned to TCDC is as high as the ACIP.

- *“We, of course, welcome another tool (referring to a new vaccine) to combat the diseases.”*
- ***Frontline dengue control workers:*** Dengue’s yearly epidemics have become a tremendous challenge for frontline dengue control workers, which include TCDC’s branch officers and staff from the municipal health department. The innate high tension involved in dengue outbreak response makes the frontline dengue control workers

support the idea of a public-funded dengue vaccine (high support 2+), but their power to impact the policy is low.

- *“We have done all we could and nothing too much could be improved. When the epidemic starts, the pressure is so overwhelming.”*
  - *“Of course, I wish that there is a dengue vaccine.”*
  - *“We’ve pushed so hard to shorten the time between a case being reported and being confirmed by the lab. The deployment of household and environmental spraying is such an immediate response that demands intense efforts and resources.”*
- ***Members of the municipal councils:*** Public vaccines are perceived as a necessity of social welfare that the councilors strive to get for the people they serve. Since local governments do not have their own ACIP, the councilors would choose vaccines that are already recommended but not yet implemented by the TCDC to be their “benefit” vaccine. The position is high support (+1), but given the jurisdiction is limited to the locality, the power is medium.
  - ***Executive Yuan and the Prime Minister’s Office:*** The Prime Minister’s office has the power to appropriate additional funds to the national vaccine fund, so the power is high. However, the Executive Yuan holds a neutral position on issues around public vaccines. There was an instance when the Prime Minister’s office rejected the MoHW’s request to increase the budget to cover the injection fees for physicians who administer public vaccines in their clinics. In another instance, the same office approved extra funds to increase the coverage of flu vaccines in the country.

- **Media:** The media has a high power to shape the vaccine policy. Their position is neutral, which means that they do not openly oppose the policy, nor do they fully agree with what the government officials say about public vaccines. The journalists have doubts about the science that demonstrates the benefit and need for a vaccine, but at the same time, they don't have strong motivations to write against it.
  - *“Through the years, TCDC has become better in messaging and public communication, we just report what was being fed to us.”*
  - *“Sometimes, I have doubt about the safety of the vaccine, but the law (infectious disease control law) stipulates that we cannot mislead the public.”*
  - *“The younger journalists are too busy to do in-depth reports.”*
  - *“We still need to verify the authenticity of the sponsored cases (referring to ads); the media needs to do good. ...But maybe we don't need so many vaccines, that is needed when Taiwan was still an under-developed economy.”*
  
- **Legislators:** Different from the councilors of municipalities, legislators of the central government generally do not advocate for more public vaccines to gain popularity. On the contrary, a few legislators are vehemently opposed to public vaccines. Two legislators, coming from the background of feminist movements, opposed to the inclusion of HPV in the NIP for fear that the symbolic meaning of HPV vaccine as prevention for the sexually transmitted virus would do harm to women's rights. The opposition softened after high level officials from the bureau of health promotion communicated the scientific evidence with them.

- *“They (the two legislators) listened and tried to understand the science. I felt like they just needed to be reassured that the agenda was not driven by corruption. I mean, they now know that we didn’t push this vaccine for benefiting anyone’s pocket.”*

Another instance when a legislator opposed to the adoption of a vaccine in the NIP, was when the legislator boycotted the proposal and questioned whether or not the TCDC did a cost-effectiveness study before the policy decision was made. The legislator withdrew her argument abruptly in the debate and allowed for the vaccine policy to be implemented.

These legislators opposed certain public vaccine policies in public. However, in private, we often see a legislator requesting a meeting with high-level officials of the government in order to advocate for a vaccine. Generally speaking, the position of legislators for public vaccines is neutral, and their power is high.

- **Hospital managers:** Hospital executives are generally physicians who are influential in the medical society in Taiwan. Hospitals, depending on their sizes and locations, would have different reimbursement arrangements with Taiwan’s single-payer healthcare insurance, the national health insurance. For those under global budget schemes, the larger the volume of service being delivered, the larger the loss the hospital would bear. In theory, hospital managers would welcome a dengue vaccine that could effectively mitigate the influx of patients during epidemics. What is paradoxical is that epidemics were often used by the hospital managers to bargain with the payer for extra reimbursement outside of the global budget limit. This happened when influenza hit the healthcare system hard during the winter. Given that the dengue epidemic could affect the incomes of the hospitals in either way, the position of the hospital managers is neutral.

The power is designated as medium because public vaccine agenda for hospitals have limited resources to affect policies in Taiwan.

- ***Leaders of the vector control program:*** After the epidemic of dengue in 2015, the government appropriated special funding to the National Health Research Institute to establish the National Mosquito-Borne Diseases Control Research Center (NMBDCRC) in April 2016 (NMBDCRC, 2016). The center serves as a think-tank to support both the central and local governments in the control of dengue. The original design of the center was focused on vector control. After several deliberations, more departments, i.e., surveillance, modeling, and clinical were added. Deviating from the original plan, the fund that normally trickled down to the hands of the entomologists became only a small portion of the allocated fund. Under the support of NMBDCRC, Tainan city had extended its existing vector surveillance control program that used “ovitrap” (Ho et al., 2005) to cover a larger proportion of the city. Leaders of the vector control programs are confident with their success and are neutral to the idea of dengue vaccine. They have moderate power to affect the vaccine policy.
  - *“I don’t think the epidemic of 2015 is going to happen again. We are doing (vector control) far better than then.”*
- ***Vector control companies:*** If a dengue vaccine program is implemented, the decreased burden of dengue does not necessarily translate to decreased job opportunities for the vector control companies. The companies sign contracts with local municipalities. When there are outbreaks, they are obliged to send teams out to the field to do household and environmental spraying and breeding site cleaning. Those jobs are very reactive and temporary in nature. In actuality, the companies’ main source of business and revenue

during most of the year are contracts for hotel cleaning, which pay better. The position regarding the vaccine program is neutral, and the power to impact is low.

- ***Bureau of Health Promotion (BHP):*** The BHP is a governmental department under the Ministry of Health and Welfare; it is a parallel organization to TCDC. Non-communicable diseases fall under the jurisdictions of BHP. The BHP is also responsible for the management of the tobacco tax. The BHP is in a difficult position. When total revenue from the tobacco tax increases, the BHP is blamed for losing the battle against smoking in the country. When the tax revenue drops, it jeopardizes the major source of funding for public vaccines. As mentioned before, a negotiated proportion of the tobacco tax is used to fund the National Vaccine Fund. A larger proportion of the tobacco tax revenues goes into the BHP to subsidize the National Health Insurance. Although BHP does not take an explicit position to oppose the adoption of new vaccine in the NIP, any increase of the negotiated percentage for the National Vaccine Fund would affect the priorities of the BHP, which is disease prevention for non-communicable diseases, such as cancer screening programs. Given this resource's internal conflict, BHP was assigned to be low support (-1) with high power.
- ***Bureau of the National Health Insurance (BNHI):*** The BNHI is a parallel organization to TCDC or BHP under the MoHW. The premium rate collected by the National Health Insurance in Taiwan is a negotiated percentage of the payroll. Over time, the growth of the payroll and the adjustments of the percentage could not catch up with the growing health expenditure as a result of new technology and a growing number of elderly citizens. One of the main goals of every Director-General of BNHI has been to contain the growth of cost to sustain the scheme. There has been discussion and push for the NHI

to cover the public vaccine program. This proposal faced strong resistance from the BNHI and its advisory committee, although the officials in BNHI are government health officials who know the value of vaccines in public health. The fact that the BNHI has the mandate to contain the growth of health expenditure indirectly put the BNHI in a position to oppose more public vaccine. In this regard, BNHI's support for public vaccine is low (-1), but power is high.

- ***Anti-vaccine movement:*** The anti-vaccine movement is relatively less influential in Taiwan compared to other industrialized countries. The two legislators that openly opposed the introduction of HPV vaccine in the NIP were coming from the women's rights perspective, so they did not oppose other vaccines. Leaders of the anti-vaccine movement advocate for transparency, informed consent and individualized decision making instead of overall vaccine recommendations that overlook personal beliefs. The position was assigned as low support (-1), and the power to influence the policy is low.
- ***Primary care physicians:*** Some of the primary care physicians who administer vaccines of NIP in their clinics have long-held grudges toward the government's policy. It was not until 2017 that the TCDC started to pay for the administration fees for public vaccines at doctor visits. The government did not cover the cost for the cold chain storage or any other fees associated with the vaccines. When there was an interruption of the cold chain, the physicians were fined and blamed by TCDC. The administration fee approved in 2017 was found to be insufficient. In 2018, the TCDC started to pay the fee by the number of vaccines instead of the number of visits. It was believed that the legislator opposed to the introduction of HepA was not really against the policy itself but was using the opportunity to bargain for more administration fees for the physicians. The position of

the primary care physician is not completely against public vaccines. If physicians were to stop providing the service of public vaccine administration, they would most likely lose their patients to a clinic that did provide vaccine administration. The position is assigned to be low support (-1), the power is low.

- *“We are not subordinate to the government in the NIP; we are partners.*
- *“Blame it to the senior pediatricians that did not fight for the fee for us; we were victims of the unfair system for too long.”*

- ***Medical Professional Associations:*** The Pediatrician Association has a long history of involvement in the government’s public vaccine policy, as the primary care pediatricians are the ones who implement the policy. Chairmen of medical associations are voted in by their association’s members, and they generally align their opinions with those of their constituents. The fact that the NIP did not pay the administration fee, nor compensate for the cost of storage for vaccines has gradually become a source of sourness between the chairmen of the Pediatric Association and the TCDC. Also, introducing more public vaccines means fewer options in the private market. Taking a quadrivalent influenza vaccine (QIV) for example, a local medical clinic could purchase one dose from the distributor for around \$15 and charge the vaccine recipient out-of-pocket for around \$35 or above. The inclusion of QIV in the public program means fewer profit opportunities for the doctors in the clinics. The position for medical professional associations is high opposition (-2) and, since it could ally with a legislator, the power to influence is medium.

- *“The government stole 1.4 billion NTD (\$46 million) from us by introducing these vaccines.”*

### 3.3. Case Studies of Selective Public Vaccine Introductions in Taiwan

#### 3.3.1. Hepatitis A vaccine

Between June 2015 and September 2017, Taiwan experienced an outbreak of Hepatitis A (W.-C. Chen et al., 2019). The risk identified by an outbreak investigation along with a molecular epidemiology study was risky sexual behavior. A HepA vaccine campaign was implemented between 2016 and 2017 and reached 16,000 individuals. A modeling study showed that the campaign was reported to have reduced the number of cases of HepA by 81% (K.-Y. Lin et al., 2019). Apart from the outbreak, the country averages between 100 and 200 confirmed cases of HepA per year.

In 2017, a philanthropic foundation, established by a construction group, offered the TCDC an ongoing donation for public vaccine funding with a commitment of ten consecutive years (B.-C. Foundation, 2020). The TCDC reviewed what was on the list recommended by the ACIP and indicated that the fund offered could cover the cost of pneumococcal vaccines for older adults. The foundation had allocated a fixed amount of money for the donation and expressed the wish to cover a whole cohort of the population under the given budget instead of a selected group for pneumococcal vaccines. The price of a Hepatitis A vaccine fits the budget. The adoption of the vaccine into the NIP was then decided with the donation in mind. Since it is illegal, according to the laws of the National Vaccine Fund, that donations made to the fund be contingent on donor-designated use, the foundation had to purchase the vaccines and donate them to the TCDC to avoid obvious violation of the law. In this case point, due to financial maneuverings, the process of adoption seemed to skip the requirements of traditional analytic frameworks.

#### 3.3.2. Quadrivalent Influenza Vaccine

The publicly- funded influenza vaccine was trivalent (TIV) until 2019 when it was changed to a quadrivalent influenza vaccine (QIV). Based on a health technology assessment report, a QIV does not perform better than a TIV in terms of cost-effectiveness in Taiwan\*. The ACIP made the decision not to upgrade to a QIV based on this finding, and the extra financial burden a QIV program might impose on the system. Since early 2019, mounting discussions of possible mismatches of the flu vaccine and the risk for a more severe outbreak were covered by the media. Legislators, based on the reports from the media, questioned the Minister of Health and Welfare about his solutions to cope with the potential crisis. Without knowing the negative recommendation made by the ACIP, the Minister announced to both the media and Congress that the government would upgrade from TIV to QIV.

### 3.3.3. Varicella vaccine

Taiwan introduced the varicella vaccine to the NIP in 2004, making Taiwan among the first countries in the world to adopt this vaccine. The vaccine was licensed in Taiwan in 1997. The then-mayor, Mr. Shui-Bian Chen, consulted with an ACIP member for a suggestion for a public vaccine, and the chickenpox vaccine was the one suggested. The policy was implemented in 1998 for one dose at the age of one. In 1998, Mr. Chen was defeated as incumbent and decided to run for President. He consulted with the same ACIP member who suggested that he consider the varicella vaccine as part of the NIP. The idea was taken and became one of his proposed health policies in the presidential campaign. Mr. Chen won the 2000 election, and the policy was realized toward the end of his first term in 2004. Although the policy was part of the President's promise made to the people during the campaign, it still needed to gain approval from the ACIP. Another important member of the ACIP experienced herpes zoster (shingles)

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\* Unpublished report, based on an interview.

during the period of discussion and suffered from the disease's complications. Some interviewees believed that the influential ACIP member's personal experience helped push the Varicella vaccine into the NIP. Despite the fact that the varicella vaccine and zoster vaccine differ in formulation, both deal with medical conditions caused by the varicella-zoster virus. The personal experience of the ACIP member facilitated the process of the recommendation.

#### 3.3.4. Rotavirus vaccine in Local Government

Some municipal governments of Taiwan have a different list of publicly funded vaccines. The list normally covers more than what the central government provides. The additional public vaccines are covered by funds approved by the local council members. Based on the data collected from the qualitative interviews, public vaccines are perceived as social welfare provided by the local government. Politicians operating in the local government get a build-up of their reputations by adding more antigens to the list already recommended by the central government. Although the local governments have their own ACIP, the members could overlap with the one that Taiwan's CDC has. This is due to the small size number of vaccine experts who are active in public policies. The process for local ACIP appraisal is less stringent than the central government process. There are even times when the decisions of local ACIP are perfunctory because the decision was made by local politicians. The processes of how PCV and Rotavirus vaccine were introduced in the public vaccine program of Tainan City is a demonstration of how Kingdon's political stream affects the policy.

In December 2010, Tainan City enlarged its geographical demarcation by merging the former Tainan City and Tainan County. The city's population grew, along with its budget. The first mayor, Dr. Ching-De Lai, announced that the city was going to offer PCV to older adults as part of his inaugural policy. The members of the council soon questioned why this policy only

benefited the older population and not minors. In response, the city announced that the government would also offer rotavirus vaccines to low-income households. As of 2019, the annual purchased doses for rotavirus was only 300, which was odd given the small number of low-income households that have young children in the city. All the doses did not get used. There were instances when the lower-income household had already paid out-of-pocket for the vaccine.

### 3.3.5. PCV13 among children

The pneumococcal conjugated vaccines were made available in Taiwan since 2006. In 2009 and 2010, the PCV7 and PCV10 were adopted in the public vaccine programs, respectively. The programs only covered high-risk groups. Since then, Taiwan experienced a high speed of *Streptococcus pneumoniae* 19A replacement, which is covered by PCV13, but not the previous vaccines. Furthermore, the highest incidence occurred among children aged 2-4 years, which is different from the epidemiology elsewhere. Given the financial constraints of the National Vaccine Fund, the members of ACIP decided to do things differently. A one-dose catch-up PCV13 program targeting 2-5 years-old was implemented in 2013, followed by one-dose catch-up for 2-5 years-old and 2-dose catch-up for 1-2 years-old in 2014. In 2015, the full NIP with PCV13 was introduced for 2, 4, and 12-15 months-old (2+1). This special catch-up vaccination program has proved to be highly effective. The incidence of invasive pneumococcal disease caused by 19A in children 0-5 years was reduced by 33 to 44% from 2012-2017 (Lu et al., 2019). A policy that started with a catch-up phase before moving into routine administration of vaccines is very unique in the world and is a proud innovation of the ACIP members.

- *“We did not have enough funds that year, this idea helped us pay one dose instead of two, and it worked.”*

The case highlights the importance of having knowledge of local epidemiology and embracing “out of the box.”

### 3.4. Mapping the Case Points to Kingdon’s Framework

We now have case points of vaccines being introduced to NIP in Taiwan. Based on literature reviews, similar data was also collected for Indonesia, Canada, the U.S., and Malaysia (Appendix 5.1-5.4). The process of the introduction of each vaccine will be used as one unit of data point to fit into the model of MSF for the development of hypotheses and the toolkit for branch companies. The table (8) shows a summary of case points being mapped onto the MSF, the star signs were marked when a particular stream was more salient in the introduction of the vaccine.

**Table 8: Mapping the Data onto the Multiple Streams Framework**

	Taiwan				
	PCV	HepA	QIV	Rota	Varicella
Problem Stream	✓	✓	✓		
Policy Stream	✓*				
Politic Stream	✓*	✓*	✓*	✓*	✓*

	Indonesia		US		Canada	Malaysia
	JE	Flu	HPV	Tdap	MenB	HPV
Problem Stream	✓	✓		✓*	✓*	✓
Policy Stream			✓	✓		✓
Politic Stream	✓*	✓*	✓*			✓*

We use Balarajan’s work to further divide each stream into three aspects for analysis and discussion as below(Reich & Balarajan, 2012):

#### 3.4.1. The Problem Stream

- **Credible Indicators:**

Understanding the burden of vaccine-preventable diseases is the first step before a vaccine is even to be considered. For example, the crucial two reports on cervical cancer burden played an important role in pushing the HPV vaccine into the NIP of Malaysia (Appendix 5.4). Invasive pneumococcal disease is not a condition well known to the general public or even political leaders. However, the knowledge of the ACIP of the local epidemiology paved the way for the introduction of the pneumococcal vaccine. The burden of JE and flu was deemed significant enough for the related vaccines to be introduced in the NIP in Indonesia (Appendix 5.1). There have been instances when a credible, objective indicator of the disease is not a necessary condition.

- **Focusing Events:**

Reports of mortality cases by the media strengthened the problem stream, regardless of how accurate the information is. News of mortality had been used as incentives for the government in Taiwan to boost the immunization rate of seasonal influenza vaccines:

*“When we see that the uptake slows down, we will include some coverage of lethal cases in the press release, it worked.”*

In the above case, the government used the media to amplify the perceived risk of disease to promote vaccine uptake. The reverse direction of this strategy also seems to be effective. In the case of Québec, Canada’s outbreaks of serogroup B meningococcal meningitis, although the public health officials knew that the true incidence of the condition had not significantly increased, the dramatic nature of the course of the disease and the people’s intense responses to media reports prompted the policymakers to react with a vaccine campaign (Appendix 5.2).

*“These are obviously very dramatic and very sad cases, but we normally have an average of eight cases, and this year has been a little bit less, four cases, including this young man.”(News, 2014)*

In the U.S, the same serogroup B meningococcal meningitis vaccines (MenB-FHbp and MenB-4C) were not approved to become publicly funded vaccines. By the time ACIP’s working group was reviewing the data, the incidence of serogroup B meningococcal disease was low and stable at around 50 to 60 cases and 5 to 10 deaths annually in the U.S. The Number Needed to Vaccinate (NNV) to prevent the death of one college student was 368,000 costing \$2.3 million, resulting in a cost per QALY of up to \$9.4 million(MacNeil et al., 2015). The vaccine program was considered not cost-effective, so it only received a Category B recommendation, which is “recommended for individual clinical decision making.” The Quebec Immunization Committee (Le Comité sur l’immunisation du Québec, CIQ) is no less transparent or less professional than USACIP. In fact, the public vaccine framework of CIQ has 58 criteria classified in 13 categories, a more comprehensive one than the EtD used by the USACIP. This demonstrates that the determining factor was not in the absolute difference of risk, but the perceived risk which raised the problem stream in Canada but not in the U.S.

- **Issue Framing:**

How disease is “framed” and how the framing is accepted by different stakeholders have impacts on the problem stream. In the case of Hepatitis A, government officials and the foundation that donated the HepA vaccine refrained from emphasizing the sexual behaviors that are associated with the outbreak in 2015-2017 to avoid stigmatization.

*“We have many people traveling to and from these Southeast Asian countries nowadays. The risk of importation of the virus through travel is high.”*

The disease was framed as a threat that neighboring countries posed to Taiwan, so the vaccine was then explicitly framed as a policy to protect everyone. In point of fact, TCDC records imported HepA only in about 20-30 cases per year (TCDC, 2014).

Another example is QIV. In 2018, the threat was framed as “the mismatched virus strain is going to render the current flu vaccine useless.” QIV was presented as the solution to counter that threat. As it turned out, the burden of influenza was not significantly higher than any other normal year\*.

As discussed in Section 2.1.4, dengue’s burden is primarily shouldered by the southern cities of Taiwan, specifically, Tainan, Kaohsiung, and Ping-Tung. Although dengue occurs in urban settings and is generally not considered a disease of the poor, the fact that the south is less economically developed and robust than the north of Taiwan could cause misconceptions about how the government allocates the resource. We will further in the following politic stream section.

Although dengue is generally known as a pediatric infectious disease, the mortality and severe cases have affected older adults more in the recent epidemics in Taiwan (Section 2.1.5). The disease’s epidemiology and the media reports on mortality rates would gradually frame the dengue vaccine to be a vaccine that protects older adults.

Both the disease and the vaccine could represent different meanings to countries because of the difference in epidemiology. For example, an HPV vaccine program met with resistance

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\* Taiwan CDC: National Influenza Surveillance System accessed at <https://nidss.cdc.gov.tw/ch/SingleDisease.aspx?dc=1&dt=4&disease=487a>

from a religious society in Malaysia (Appendix 5.4), for fear that the program would symbolize the promotion of promiscuity. As mentioned before, this same program drew critics from the feminist's movement in Taiwan, for fear that emphasis on preventing sexually transmitted infections among young women would bring stigmatization.

We can see how disease and its vaccine are presented or “framed” could either facilitate or become a barrier for the vaccine to be adopted into NIP.

### 3.4.2. The Policy Stream

- **Policy Community Cohesion:**

The circle of technocrats and academics that influence the vaccine policy in Taiwan is not a large one. Out of the 17 members of ACIP, 11 are pediatricians, among which 8 are pediatric infectious disease specialists. This small circle of experts could be described as strong proponents of vaccines and are in the core group of ACIP.

According to one interviewee, the TCDC has long been reluctant to have ACIP make decisions by voting. In most of the cases a public vaccine policy was made based on a consensus decision (Section 2.1.7). One exception was when the ACIP needed to choose between PCV vaccines from two different companies. Even though the vote was close, there were no major conflicts.

- **Guiding Policy Institution:**

The guiding governmental institute of public vaccine policy is TCDC. Although there is Center for Drug Evaluation (CDE), a quasi-governmental organization that does cost-effectiveness studies for new drugs, the organization does not function at the same level as the National Institute for Health and Care Excellence (NICE) in the UK. TCDC can proactively assign tasks to CDE for vaccine evaluation. The leading academic institute is the Pediatric

Infectious Disease Society, which has a long-standing history of working closely with TCDC for vaccine policy and infectious disease prevention consultancy. The two institutes generally converge on issues of public vaccines. Experts from the society also help TCDC communicate with the public (Section 3.2).

- **Viable Policy Alternatives:**

In the case of PCV13's introduction in Taiwan, a viable policy alternative to prevent the invasive pneumococcal disease among children aged 2-5 y-o was proposed by the experts of the ACIP. The domain knowledge that the ACIP has can determine whether the policy options could be created. When faced with the burden of pertussis that occurred among infants aged less than 2 months, The U.S. ACIP first recommended vaccinating unvaccinated postpartum mothers and other family members, a schedule referred to as cocooning (Appendix 5.3). The difficulty of implementing the cocooning strategy led the ACIP to further recommend that the unvaccinated pregnant women receive Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine). Creating options that were not originally promoted by the vaccine manufacturers takes an innovative mind. However, not every country's policy environment is favorable for such kind of alternatives. In Canada, a schedule of two doses of PCV10 followed by a toddler dose of PCV13 was recommended, but the government faced difficulty in negotiating the contract of procurement, and the policy alternative had to be dropped (De Wals et al., 2019). This shows that the policy stream alone cannot guarantee the success of policy adoption.

According to Kingdon's MSF, viable policy alternatives must be concretized and prepared in place before waiting for a policy window to open. Given that the lifetime of a policy window is short, an alternative that is not well articulated can't be proposed as a solution when a

problem arises. Applying the above findings to dengue vaccine strategy, the viable policy alternatives that the LOCs need to review as policy alternatives will be:

1. Single-dose administration of TDV for outbreak response (particularly DEN1 and DEN2)
2. Sequential administration of TDV with Dengvaxia
3. Joining the TDV as a complementary tool to the existing Integrated Vector Management in the targeted country.

- **Policy Entrepreneurs:**

The definition of “policy entrepreneur” is an entity or an individual from the policy community circle that could bridge the gap between technocrats and bureaucrats and develop a policy that is feasible and implementable. In Taiwan’s situation, the technocrats and bureaucrats have very close working relationships, making an individual policy entrepreneur less relevant. In other places of the world, a third party other than the ACIP or the government needs to play a role to promote a set of policy solutions and proactively bridge both sides. Such a third party could be a legislator who sponsors a law or an NGO from the civil society. In the case of Taiwan, key ACIP members hold different positions, including chair of the academic or medical professional society, making the distinctions between these roles blurry.

In the case of Malaysia’s HPV immunization program (Appendix 5.4), the “public health specialist association” played a role that bridged the government and the academic institutions. In the case of U.S. HPV immunization for the school-entry mandate (Appendix 5.3), the “Women in Government (WIG)” served this role. Both the public health specialist association and WIG received funding from the industry to champion the policy.

### 3.4.3. The Politics Stream

- **Political Transitions:**

Political continuity does not affect a public vaccine policy once the vaccine is already on the list of NIP. Since the public vaccine is considered to be social welfare in Taiwan, it is difficult for any politician to even think of taking away what has already been implemented.

However, political continuity does affect a policy that is still in incubation. The HPV immunization program was on the table for discussion in Malaysia's ACIP for years (Appendix 5.4). The ACIP was attended by the Director-General of the Ministry of Health. Once the policy gained the buy-in of the DG, the DG still needs to communicate with the Ministry of Finance or escalate it to the Cabinet. In such circumstances, political continuity is important so that a "slow cooking policy" option does not get interrupted. However, the political transition can also open a policy window for a new vaccine to be adopted when a newly elected politician announces a new vaccine as his/her policy. This is supported by the cases of Tainan's introduction of PCV and rotavirus vaccine, and Taipei's introduction of the varicella vaccine. According to one interviewee, Malaysia's recent adoption of PCV happened within one year after a new administration took power. Historically, it was always different stakeholders pushing the MoH to adopt a new vaccine, but in Malaysia's PCV, it was the MoH's high-level officials who championed the policy.

A political transition could either interrupt or open policy windows for public vaccines. In 2019-2020, the presidential election politicized dengue control in Taiwan. The Mayor of Kaohsiung, Kuo-Yu Han, challenged the incumbent, President Tsai, for the presidency soon after being elected Mayor. Kaohsiung's dengue epidemics became the target of critics when Mr. Han was portrayed as a run-away Mayor who was not capable of delivering services to his

constituents. In response to that, Mr. Han climbed a tree before twenty journalists as an effort to do a “breeding site inspection.” The video went viral, and discussion around vector control soon turned political. Mr. Han claimed that the central government was conspiring to allow the dengue to get worse in order to make him look bad. As a reaction, the Executive Yuan appropriated a large fund to help vector control in Kaohsiung. If an approved, recommended dengue vaccine were in place, the fund could have been used for purchasing the vaccine. Elections, campaigns, and political transitions are considered policy window in Kingdon’s MSF.

- **Hidden Alliances:**

Identifying hidden alliances through political thinking is described as a leadership skill by Heifetz (Heifetz, Grashow, & Linsky, 2009). Merck used this tactic to ally with Women In Government (WIG), whose goal as an organization was to fight cervical cancer. It is not clear whether Merck influenced WIG’s agenda to comply with its HPV commercialization agenda, or if it was an incidental synergy. Sanofi lodged its appeal to the Presidency of the Philippines to regain its license after news revealed that the President’s daughter had contracted dengue. Malaysia’s HPV immunization program gained traction when the Prime Minister experienced bereavement due to cancer. Similarly, Taiwan’s varicella public vaccine inclusion was pushed by one important ACIP member who had contracted zoster. The above examples show that potential alliances for policy often exist because someone’s personal experience sensitizes him/her to appreciate the policy more. According to one interviewee, Taiwan’s Methadone Harm Reduction policy received fierce resistance from legislators. The leadership of TCDC identified a legislator who had a family member who suffered from drug addiction. By forming an alliance with this legislator, TCDC established a coalition and got the policy implemented.

Only one out of the 17 members of Taiwan’s ACIP lives in the geographical area at risk for dengue. This person’s experience in managing the overloaded hospitals during the dengue outbreak would make him a good candidate as a policy ally. The above examples show that resistance to a policy could be obvious, but potential alliances are sometimes hidden and take effort to be identified.

- **Political Ideology and External Influences:**

The JE vaccine and influenza vaccine cases in Indonesia (Appendix 5.1) show that political ideology affects public vaccine policy. In these cases, the ideologies were nationalism and protectionism. The Indonesian government rejected the introduction of a public vaccine based on the fact that the vaccines were imported as opposed to being manufactured locally. Taiwan does not have such a policy and is still importing vaccines for its NIP. However, from the results of our interview data, a theme of nationalism has been identified:

- *“Since 1998’s enterovirus outbreak, we have been talking about having our own vaccine industry....now look at China, they already have three enterovirus vaccines licensed.”*
- *“Korean was lagging behind us, but now they can export... they spend more on vaccine per capita than us...”*
- *“Look at our HBV vaccine program, the first one in the world....we are no longer the leading...that is the legacy.”*

Public vaccine policy was described as “national pride or glory,” according to some interviewees, that we should not let fade. Such a proud ideology paves a common ground for technocrats and bureaucrats to strive to provide the public with more public vaccines. Since they are colored by nationalism, external references are important.

- “We follow what the U.S. ACIP says. WHO is more for the developing countries, but we have moved beyond that level long ago.”
- “We ranked behind a lot of countries in the world in introducing the HPV in NIP, that is so late.”

Unlike countries in Latin America, where getting WHO, SAGE, and PAHO’s recommendations are among the first steps for a vaccine to get into the NIP, Taiwan follows USACIP more closely. However, it is not clear if there is an exception to the dengue vaccine. Since the U.S. is not endemic to dengue and the ACIP deliberations around Dengvaxia are focused on the scenario in Puerto Rico.

### 3.5. Key Insights and Discussion

#### 3.5.1. The Ethical Principles of Public Vaccine Decision

The idea of having experts review the cost-effectiveness and burden of disease to decide which vaccine program to prioritize is conforming to the ethical principle of *objective utilitarianism*. Different from the *subjective utilitarianism* described by Bentham that treated the utility as a decentralized, self-defined metric to everyone (Bentham, 1970), *objective utilitarianism* adopts a centralized, collective approach to define the goal of a policy. In the case of public vaccine policy, the collective goals refer to DALY, QALY, or simply the decrease of incidence and burden of certain disease. The principle is the basic thinking behind the cost-effectiveness or related health economic studies. The single metric has limitations in terms of taking individual preferences into consideration. Further, not all cultures value health outcomes in the same way. The *future discount rate* for the benefit of a vaccine policy is another issue. Some vaccine policies generate a benefit far later than others. For example, the effect on the

decrease of cervical cancer incidence of an HPV immunization program happens in the far future, compared to the effect of a meningococcal vaccine on the incidence of meningococcal meningitis, which is much more expedient. Applying a higher future discount rate would make the HPV vaccine program much less appealing, and this part of the consideration is generally not made clear in the analytical frameworks of public vaccines. The last issue concerns equity. As the authors of *“Getting Health Reform Right”* put it: “A final problem for health reformers who consider the utilitarian approach is the ruthlessness implicit in the position’s commitment to producing the largest gain for the available resource—regardless of the fairness or equity of the result (Roberts, 2008, p. 48).” Following utilitarianism’s collective metric to measure the success of a policy leads to the extreme scenario often depicted in an ethics class such as: “ Passengers who are starving on a lifeboat could kill and eat a few of their fellows, provided the gains exceed the losses(Roberts, 2008, p. 48).” The arguments made to promote the use of Dengvaxia to gain public health benefits, overlooking the risk for a small number of individuals, adopted the similar logic of utilitarianism (Meissner, 2019). The analysis shows that the language of the technocrats of vaccine policies is closest to objective utilitarianism, while that of the politicians is closer to egalitarian liberalism. The actual adoption of a policy is based on a mixture of the above values, but both the value principles and the priorities set by the ACIP could be trumped when political streams become the salient factor.

### 3.5.2. Why politics?

One stream that stands out from Kingdon’s Multiple Stream Framework when applied to public vaccine agenda setting is the political stream. “The literature on policy analysis has firmly established that policy changes are not simply a technocratic process based on rational analysis and that knowledge alone is not sufficient for policy change. The policy change is a profoundly

political process."(Reich, 1995). Kieslich and colleagues further wrote: "Against the background of one prominent definition of politics as the study of who gets what, when, and how, priority setting can be viewed as fundamentally political because of its distributional consequences... Even priority-setting institutions designed to moderate political pressure by basing decision making on economic analyses and transparent processes consist of complex political processes involving many stakeholders who may hold different values and worldviews." (Kieslich, Bump, Norheim, Tantivess, & Littlejohns, 2016). The decision-making tools for prioritizing vaccine in the public vaccine agenda provide a framework for decision-maker support, but would not sufficiently allow us to understand why decisions were made. As described in the case of Taiwan, one vaccine fulfilling more of the criteria listed in the analytic frameworks mentioned in the 2.1.9 section might be adopted later than the one that fulfills less. Without the lens of politics, it is difficult to comprehend or predict the process and endeavor to strategize politically. " People who think politically discern the formal and informal exercise of power and influence among individuals in their organization.\*" (Heifetz et al., 2009). When we expand this political thinking from the personal leadership arena to vaccine policymaking, the principles still hold true.

### 3.5.3. Spillover effect

The spillover effect was described by Kingdon as "Once a precedent is established in one area, it can be used to further a similar change in an area that is like the first in some way." (John W. Kingdon, 1984, pp. 200-204). The author used federal legislation in the U.S. as an example, "the passage of the first auto safety legislation resulted in a parade of safety legislation in flammable children's clothes, coal mines, and other diverse fields, culminating in the Occupational Safety and Health legislation." The author attributed three factors that could

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\* Prof. Ronald Heifetz of Harvard Kennedy School of Government

explain such an effect. The first factor is the behavior of the legislator. In the case of some auto safety legislation, "the Congress ran through all the safety issues in very short order because the first of them had hit and was a political bonanza for its sponsors." The Congressmen who were inspired by the first success of their colleagues might start searching for the next win in the adjacent fields to harvest political popularity. The second factor is if a first case becomes an argument of analogy for a second case. Finally, the third factor is when the resisting coalition was weakened in the process, so it could be transferred to issues of a similar nature.

The municipal government of Tainan's introduction of pneumococcal vaccine and rotavirus vaccine could be examples of the spillover effect. The first and second explanations are a better fit. Once the legislator observed the political effect of adopting the pneumococcal vaccine, he/she turned to the rotavirus vaccine to seek the same result. Using the spillover effect to describe the public vaccine adoption is non-existent in the literature (to the knowledge of the author). It provides a cue to seize the opportunity of a policy window, which could otherwise be difficult to come by. However, such an application is not without caveat, as the window that opens after the first success often shuts down rapidly. This is because the policy implementation could uncover problems. "The precedent-setting ideas must be extended to other areas fast because the argument for doing so may erode as time passes." Apart from Tainan's example, it is rare to see the introduction of one vaccine relating to another. However, the idea could be applied to the venue through which a vaccine is implemented. In the context of dengue vaccine introduction, the school-based immunization is one of the most feasible ways to ensure coverage. If the HPV vaccine programs paved the way for vaccines to be used in school-based settings in a target country, the policy window would be opened for Takeda to introduce TDV through the platform of school systems throughout the country.

#### 3.5.4. Cui Bono?

“Cui bono” is a Latin phrase meaning “who stands to gain?” Peter Blau, an influential sociologist who transformed the study of social inequality and mobility, often asked this question, “cui bono?” in his works (Scott & Calhoun, 2004). The beneficiaries of the vaccine have significance when looking through the lens of political economy analysis. As described in 2.1.11, since the early 1990s, the World Bank has put efforts to shift the focus of global health from child health to adult health. According to Reich’s analysis, all five political streams favored child health over adult health (Reich, 1995). Whom a vaccine policy is going to benefit has a significant impact on the policy, which is described as the “symbolic politics stream.”

Similar to the World Bank’s effort, there is a push to expand the use of vaccines from infant and child protection to adults. The movement is named the “life-course immunization.” In May 2012, 194 member states of the World Health Assembly endorsed the WHO Global Vaccine Action Plan 2011-2020 (GVAP) and declared a “Decade of Vaccines.” (WHO, 2012b). The plan includes a focus on establishing a life-course approach to immunization beyond childhood and into old age (Thomas-Crusells, McElhaney, & Aguado, 2012). Such an approach is not only meant to protect the elderly against vaccine-preventable diseases, but also covers pregnant women, adolescents, and adults (Philip, Attwell, Breuer, Di Pasquale, & Lopalco, 2018). Takeda conducted its phase three clinical trials for the dengue vaccine among children and young adults, which means that the indications on the label will be limited to these age groups. Unless a further study, such as immuno-bridging, was conducted to expand the indication, the vaccine would be used to benefit children and young adults, but not adults or older adults. Given the changing epidemiology and burden of dengue toward the older age group described in Section 2.1.5, how the vaccine is “branded” has not only a scientific meaning but

also a symbolic one. Since mortality cases of dengue occurred mainly among older adults, the disease is perceived as a threat to the older population in Taiwan. Adoption of the dengue vaccine has the symbolic political meaning of benefiting the elderly, which will translate to a platform that is easily understood and used by politicians, according to their liberal egalitarian approach.

### 3.5.5. The Analogy between Influenza and Dengue\*

The comparison of dengue and influenza is useful for us to understand how the disease nature could affect the risk perception and, in turn, affect the behaviors of vaccination.

- **Cyclic epidemic**: In Taiwan, both dengue and influenza have seasonality. Dengue is re-introduced every year between May and September. (Lo, 2015). People living in endemic or hyperendemic areas of dengue know that the epidemic is predicted for when the temperature rises during summer and rainfall increases during the rainy season or due to typhoons. The transmission is predictable by the public. Similarly, flu season is in winter, while some places in the world experience a minor peak of transmission during summer. The cyclic patterns of both flu and dengue might be considered by people living in endemic regions, “just a part of life.”
- **Mild disease course**: The majority of the infected cases of dengue have self-limited symptoms or are even asymptomatic. It was estimated that between 50-100 million people have dengue infection annually in the world, while only around 10,000 to 20,000 die (WHO, 2019a). Using statistics for influenza in the U.S for 2017-2018, between 9 to 45 million, became ill, while the number of deaths numbered only between 12,000 to 61,000 (CDC, 2020). Given this figure, the majority of the general public might not know or hear of

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\* The author wants to thank the supervisor at Takeda, Dr. Ted Tsai, for his insights on this topic.

someone that dies as a result of influenza or dengue. Remarks such as: “I had flu/dengue, but it seemed ok” might not be uncommon.

- **Complacency:** Since the epidemics are seasonal or at least repeatable every year, and the majority of the infected have a relatively self-limiting disease course, complacency set in. It is not uncommon to hear people say: "I never got the flu shot but never had the flu either." The same statement could well be applied to dengue. The complacency could evolve into apathy regarding prevention measures, such as vaccines. The seasonal flu vaccine coverage rate among healthcare professionals (HCPs) is generally unsatisfactory if it is deemed optional. However, legally making it mandatory might result in pushbacks from the professional society, such as in a case in Canada (Jackson-Lee, Barr, & Randall, 2016). Being equipped with the medical knowledge of flu did not decrease the resistance or reluctance to receiving a flu shot among the HCPs. It could probably be explained by the large amount of relatively mild symptoms they treat daily. Complacency leads to apathy or even resistance, which could be the largest opponent to market access.
- **Media attention:** Infectious disease-related events seldom make the headlines, whether it is in developing or developed economies, except for the novel, emerging threats of a pandemic, such as COVID-19 caused by the novel coronavirus, H1N1 pandemic flu, or SARS. For other vaccine-preventable diseases such as cervical cancer (HPV), zoster, rotavirus infection, invasive pneumococcal disease, or meningococcal meningitis media coverage is relatively rare. Dengue and influenza are different. Although the yearly epidemics are anticipated, case number and death tolls would receive major coverage and thus lead to public attention. According to discussions in Section 3.3.2 and 3.4.1, media coverage can shift the problem stream and result in agenda change.

- **Confusing symptoms:** Both diseases share clinical manifestations with other viral diseases. Flu resembles other upper airway infections, while dengue could be confused with chikungunya, zika virus infection, or other non-vector borne viral infections. It is uncommon to hear the general public questioning: “I got a flu shot, why did I still get the flu?” Although breakthrough infections do happen, those who contract a viral infection that mimics the presentation of flu or dengue might blame it on the imperfect efficacy of the vaccine, or simply consider the effort “not worth it.”
- **Complex recommendations:** The flu vaccine recommendations evolved with time to incrementally cover populations from different age groups and of different underlying risks. No other vaccine program has gone through so many iterations. The targeted population of the flu vaccination program in Taiwan is a combination of age, profession, school year, co-morbidity, pregnancy status, and parental status. The eligibility by different characteristics for public flu vaccination is unique, but the future dengue recommendations could be comparable. WHO’s SAGE currently recommends that countries or localities with seroprevalence of dengue above 80% at 9 years-old to consider vaccination programs without pre-testing. For those below 80%, a serological test to limit the use among the seropositive was required(SAGE, 2018). Such recommendations have already increased the difficulty of the implementation of a dengue vaccination program. Moreover, given the size of the population at risk, countries that plan to provide dengue vaccine in their NIP would have to consider incremental catch-up by age or prioritize the more vulnerable, as the recommendations by risk groups. In this case, we might see a similar evolutionary pattern of dengue recommendations like the ones for influenza. The above analogy suggests that the policymakers who wish to plan for a dengue vaccination program could consider population

access, implementability, financial implications, and public communication in order to address complacency and resistance issues by referring to their existing influenza immunization program.

### 3.5.6. The Perception of Risk

There is a gap between the risk of disease assessed by data science and the risk perceived by different stakeholders. It is desirable for the former to impact the decision-making of vaccine policy. However, the latter equally, if not more, influences the policy. Paul Slovic used psychometric analysis to theorize that the perception of risks is associated with two factors: the absence of knowledge regarding the hazard (risk unknown to science, unknown to those exposed), and the dreadful character of the hazard (fatal, involuntary, or uncontrollable). The seminal paper of Slovic used the theory to explain why communication of risk based on objective data does not help people process the risk they perceive. Comparisons such as: “the annual risk of living near a nuclear plant is equal to riding three extra miles on an automobile” do not address the fear the nuclear plant poses on its neighbors (Slovic, 1987). The theory explains why the tetanus vaccine ranks higher in “willingness to be vaccinated” than the influenza vaccine, even though influenza has a higher burden of disease, complications and mortality rate. Tetanus has an infamous, spectacular, and dramatic manifestation compared to flu. The problem stream of Kingdon’s MSF takes the perception of risk and its political implications into account.

Daniel Gilbert used psychology and human evolutionary behavior to explain why the threat of climate change fails to gain attention (Gilbert, 2010). The policymakers that deal with the public’s perception of risk toward the vaccine-preventable diseases can draw from literature coming from environmental health studies. Gilbert stated that the 4 “I”s that draw the attention of

the public are: Intentional, Immoral, Imminent, and Instantaneous. Climate change fails to gain enough attention because compared to terrorism:

1. It does not have a villain figure with immoral intentions
2. It kills insidiously, unlike a bomb
3. The impact is far in the future, not now.

In this regard, the perception of risks in vaccine-preventable diseases differs by the nature of the disease. The threat of potential cervical cancer in the future as a result of HPV infection is not comparable to the speedy death caused by meningococcal meningitis. However, media coverage and rumors can amplify or modify the perceived risk of certain infectious diseases. The perceived risk could be arguably different had the origin of COVID-19 not been speculated on as the result of a leakage of a bioweapon (intentional) or consumption of wildlife (immoral). The implication of public vaccine policy is that governments tend to be reactive to the public's fear, which is a result of the perceived risk of disease. When an epidemic and its related deaths are understood as imminent and instantaneous, the policy window is opened for agenda change. De Wals and colleagues used the three meningococcal outbreaks in Canada, of which Québec was an epicenter, as an example. "The pressure from the public, motivated by panicking sentiments, led to the launch of mass campaigns of new or unfamiliar vaccines, despite that the total number of cases was low (De Wals et al., 2019)."

### 3.5.7. How Beneficent is the Market?

RA Easterlin in his work: "Is the market beneficent? " listed a few arguments on how we can't rely on the force of the free market to make a vaccine available to the public:

1. **Knowledge.** He used the example of the anti-vaccine movement for the argument that not everyone has the necessary knowledge and judgment to know how a vaccine is beneficial to one's health.
2. **Price.** Even if one has the knowledge, he/she might be priced out when the vaccine is costly.
3. **Principal-agent problem.** A baby would rely on the parent to make immunization decisions on his/her behalf.
4. **The free-rider.** People, after benefiting from the protection of herd immunity, might have less motivation to be vaccinated (Easterlin, 1999).

Easterlin ended the paragraph by citing a World Bank publication: "Had it been left to private markets during the last few decades. It is inconceivable that today some 80 percent of the world's children would be immunized against the six major-vaccine preventable childhood diseases" (Musgrove, 1996, p. 14).

What is the definition of the health system? The most frequently used definition of the health system is from the World Health Organization's World Health Report 2000 (WHO, 2000), which defines a health system as "all the activities whose primary purpose is to promote, restore or maintain health." The activities were classified into six categories, the building blocks of the health system:

1. Service delivery
2. Health workforce
3. Health information systems
4. Medical products, vaccines, and technologies
5. Health systems financing

## 6. Leadership and governance (WHO, 2012a).

A typical classroom debate coming from the studies of public health would be: if a publicly-traded pharmaceutical company has the fiduciary responsibility to maximize shareholder's profit as its primary goal, then is it still considered part of the health system? Ledley and colleagues conducted a cross-sectional study to compare the annual profits of 35 large pharmaceutical companies with 357 companies in the S&P 500 Index from 2000 to 2018. The study found that the median annual profit margins of pharmaceutical companies were significantly greater than those of S&P 500 companies (76.5% vs. 37.4%) (Ledley, McCoy, Vaughan, & Cleary, 2020). The authors proposed to use this study as the basis for evidence-based pricing reform for medications. Their conclusion reflects that the general sentiment toward the industry for their role in public health has been a love-hate relationship. Based on the eight-month field assignment with the host organization, the author believes that the industry's participation plays an indispensable role in making the access of treatment available to a larger population in an expeditious way. The processes include the development of the product, conducting clinical trials, pursuing licensure, development of strategy for recommendations, and eventually the commercialization and marketing of the product. The beneficent aspect of the market is that it provides the necessary resources for the above activities to be conducted. Without these processes, there would be no population access to immunization.

### 3.6. Contribution to the Host Organization

The Global Office of Immunization Science and Policy is working with Regional Medical Affairs and the Global Office of Commercial to develop tool kits that would inform the action plans for the local operating companies (LOCs) to prepare for the dengue vaccine launch. Except for the domestic market in Japan, Takeda has no vaccine assets in the global market, nor

does it have a sales task force that is experienced with a vaccine-related market access strategy. Among the countries that are listed as wave 1 (the prioritized markets), some existing LOCs are yet to hire personnel designated to vaccine-related affairs. Using the political economy analysis to understand how NITAG's public vaccine policymaking process is influenced by socio-economic and political factors would offer the LOCs another angle of analyzing the recommendation behavior of the NITAGs. Such insight is necessary for the preparation of policy alternatives and for identifying the policy window when it opens. On the other hand, it is helpful to know why there is no policy window for the dengue vaccine's introduction. According to our discussion in 2.1.11, if the politicians, after the calculation, deem the policy politically infeasible, there will be a lack of motivation, which is described as the politician politic stream by Reich. Building upon Balarajan's work (Reich & Balarajan, 2012), the thesis summarized the data and fit it into sub-themes in each stream as below:

1. Problem Stream: 1. Credible Indicators 2. Focusing Events 3. Issue Framing
2. Policy Stream: 1. Policy Community Cohesion 2. Guiding Policy Institution 3. Viable Policy Alternatives 4. Policy Entrepreneurs
3. Politics Stream: 1. Political Transitions 2. Hidden Alliances 3. Political Ideology and External Influences

Based on the above work, a set of questions was designed around the dengue vaccine scenario by each sub-theme as a tool (Appendix 5.5) provided to the company. The toolkit questions, along with the case study of Taiwan's public vaccine introduction, would help the LOCs approach the issue through the perspectives of the political economy analysis.

### 3.7. Contribution to the Studies of Public Health

Political economy analysis has been applied widely in the studies of health agenda setting, but those that focus on public vaccine decision-making are rare. The thesis demonstrates that the traditional framework analyses for the public vaccine (Section 2.1.9) fall short in examining the socio-cultural, political, and economic contexts for policy considerations. Analytic frameworks for health agenda setting such as stakeholder mapping using forcefield mapping (section 3.2) and Kingdon' multiple stream frameworks (2.1.11) were utilized in this thesis in analyzing the policy processes of public vaccines. The revised version of Kingdon's MSF, that divides the politic stream into five sub-streams, provides extra insights into understanding the impact of "cui bono" through the symbolic politic stream (section 3.6.4), and how politicians make decisions through the politician politic stream (Reich, 1995; Reich & Balarajan, 2012). Finally, applying the literature from environmental health and climate change to understand the perception of risks through the lens of behavioral science helps to broaden the studies of vaccine acceptance.

## **4. Conclusion**

### 4.1. Summary

Dengue infection is a communicable disease that poses a serious threat to global public health. The only FDA approved dengue vaccine failed to provide protection without safety concerns. Once a safe and efficacious dengue vaccine is registered, there are still steps to take before the vaccine could be made available to the population and make a positive impact. Waiting for recommendations from the public vaccine advisory bodies is the hold-up that could cost the public years without a vaccine. In this eight-month field assignment with Takeda Vaccine Business Unit, Taiwan was used as an example to understand the processes of public vaccine decision-making through the lens of political economy analysis. Other vaccines'

introductions in the U.S, Canada, Indonesia, and Malaysia were added as case points to demonstrate that socio-cultural, political and economic factors could influence public vaccine policies. Findings from the analysis include:

1. The language of the technocrats of vaccine policies is close to the *objective utilitarianism*, while that of the politicians is close to the *egalitarian liberals*. Both value principles could be trumped when politics stream becomes the salient factor.
2. The perceived risk of diseases could impact the policy. It is translated into a sense of urgency to provide momentum for policy change.
3. The concept of “Cui bono?” or “Who stands to gain?” could impact the public vaccine agenda through the symbolic politic stream.
4. Personal experience of the policymakers matters as hidden alliances could be established or leveraged.
5. Political ideologies such as nationalism or protectionism could play a role.

After the cases from example countries were applied to Kingdon’s MSF, a toolkit of questions based on the MSF was developed for the company’s country branches to utilize. The tool questions, along with the examples, would help the staff familiarize themselves with the political economy analysis to broach public vaccine policy issues.

#### 4.2. Proposals for Future Investigation.

Processes of public vaccine adoption are idiosyncratic by country. It takes theories from political science, social science, organizational behavioral science, and other interdisciplinary approaches to effectively dissect the anatomy of the policymaking processes. Quantitative

methods fall short in this regard. Although key stakeholders that are familiar with the public vaccine processes could be rare and difficult to engage, data generated from qualitative interviews with them can bring insights not revealed in the literature before.

Vaccines, along with medicine and technology, were considered one of the building blocks of the health system (WHO, 2000). Studies of the health system rarely include immunization and the role of pharmaceutical companies as an integral part of the system. Further research of the policy involvement from the industry would add value to the literature of health system research.

## **5. Appendix**

These case points demonstrate the challenges of studying the processes of vaccine adoption in a given country. The determining criteria through which a public vaccine decision was made differs by socio-political contexts and backgrounds. Sometimes, speculation and assumptions were made in order to explain the decisions. Even if those speculations could be supported and lead to a summarized description of a country's vaccine adoption behavior, the summary is still based on limited cases.

### **5.1. A Case Study of Indonesia's Public Vaccine Adoption**

Hadisoemarto and colleagues conducted in-depth interviews with 13 key stakeholders in Indonesia to understand the public vaccine policymaking of the country (Hadisoemarto, Reich, & Castro, 2016). The study used a pentavalent vaccine's introduction into the NIP and four other vaccines (Japanese encephalitis vaccine, rotavirus vaccine, influenza pandemic vaccine, and polio IPV) that failed to be included to hypothesize the necessary and sufficient conditions for a

vaccine to be adopted. The analysis of the first two vaccines that were not approved is noted as below:

- JE vaccine: The evidence that supports the vaccination against JE in Bali, Indonesia was published in 2006. The evidence was presented to the Ministry of Health the same year and gained strong support for the immunization program in Bali. An immunization program using a live attenuated vaccine from China was proposed in 2007. The affordability of the Chinese vaccine made the program appealing and feasible. The program was rejected by the Minister of Health, because the minister did not want to use imported vaccines in the NIP.
- Influenza pandemic vaccine: WHO made available a total of 122.5 million doses of influenza pandemic vaccine after it declared the pandemic status of H1N1 in June of 2009. Indonesia was eligible for the donation. However, it was reported that the parliament urged the Ministry of Health to refuse the donation. The Ministry of Health was concerned about the long-term availability of the vaccine after the donation was made.

Summarizing the processes of five vaccine's approval or disapproval in the NIP, the author proposed five hypotheses for successful vaccine introduction in Indonesia:

1. An official evidence-based recommendation is a necessary condition for introduction.
2. Sufficient domestic financing to pay for the delivery of a new vaccine is a necessary condition for introduction.
3. Demonstrating national production capacity for a new vaccine is a necessary condition for introduction.
4. Political support is a necessary condition for new vaccine introduction.

5. The four conditions are jointly sufficient for introduction.

These five hypotheses demonstrate the role political economy plays in the policymaking of public vaccines. There are very limited publications in the literature that investigate multiple vaccine introductions in a given country and summarize the behavioral pattern.

## 5.2. A Case Study of Canada's Meningococcal Vaccine Adoption

Québec, Canada, experienced three outbreaks of meningococcal disease in recent years (De Wals, 2019). Although the absolute number of individuals being affected by the disease was low, the nature of the disease's manifestation made the events highly visible. Back then, there were only two vaccines approved for the prevention of the circulating serotype, serogroup B. They were the first two protein-based meningococcal vaccine "4CMenB" and "MenB-FHbp. Since the approval was based on immunogenicity data, evidence of efficacy and safety were still lacking. In response to the mounting pressures from the press and the panicking general public, the public health authority made a recommendation on a massive campaign for the immunization against meningococcal serogroup B. The local government spent \$10 million and procured 130,000 doses, while the vaccines were previously recommended only for high-risk group of people (De Wals et al., 2019).

## 5.3. Case Studies of the U.S.'s Public Vaccine Adoption

### 5.3.1. School-Entry Mandate of HPV Vaccine

It is ethically appealing to consider the vaccine policy process to be insulated from the influence of private industry (Mello, Abiola, & Colgrove, 2012). In this case study, we wanted to

look at the policymaking involvement of the industry in the US. In 2006, the FDA approved the first vaccine against HPV, Gardasil, produced by Merck. Within a year, legislation relating to the vaccine was introduced in 41 states, including 24 states that would mandate HPV vaccination for 6<sup>th</sup>-grade girls. Mello and colleagues interviewed 73 key informants from 6 states (California, Indiana, New Hampshire, New York, Texas, and Virginia) to investigate the role the company played in state HPV vaccination policymaking (Mello et al., 2012). The result showed that Merck promoted school-entry mandate legislation by:

1. ***Providing information:*** Some state legislators work part-time with lean staff resources and, in most states, the legislators do not have close working relationships with health department officials. The above factors forced the legislators to rely heavily on the industry to provide information about the characteristics of the vaccine and cervical cancer.
2. ***Lobbying and presenting policy alternatives to legislators:*** Some respondents reported that Merck representatives proposed specific legislation and even drafted a bill to seek a sponsor. The efforts were focused on the legislation for the school-entry mandate for HPV vaccination. Such activities were not deemed usual for the respondents of the study.
3. ***Mobilizing legislators, stakeholders, and the public:*** Merck worked with an NGO, Women in Government (WIG), to promote the agenda among the legislators associated with WIG. Merck provided unrestricted grants to WIG to host educational activities for legislators in appealing destinations. A “legislator toolkit” containing materials for the school-entry mandate bill was provided to attendees. Many of the mandate bills were introduced for consideration by members of WIG as a result. Although WIG had

identified cervical cancer as a priority issue as early as 2003, it is not clear whether Merck had driven the agenda of WIG or found synergy with it.

4. ***Filling gaps in access to the vaccine:*** Merck established a patient assistance program to donate vaccines to low-income or uninsured individuals.

The policymaking involvement strategy of Merck was described as “*overly aggressive, not fully transparent, or not divorced from financial contributions to law-makers risks undermining the prospects for legislation to foster the uptake of new vaccines.*” In summary, Merck’s vaccine introduction strategy included evidence generation and provision, using the intermediary organization to provide a legislative toolkit and draft the bill for legislators.

#### 5.3.2. Recommendation for Tdap in Pregnant Women

Infants <12 months had a substantially high rate of pertussis and the largest burden of pertussis-related death. The majority of the pertussis cases occurred among infants <2 months, who were too young to receive a vaccination. Since 2005 the U.S. ACIP recommended vaccinating unvaccinated postpartum mothers and other family members to protect the newborn, a method referred to as cocooning. After five years, the difficulty in implementing the cocooning strategy led the ACIP to recommend that unvaccinated pregnant women receive Tdap in 2011 (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine)(CDC, 2011). Both the most important features of a vaccine recommendation, safety and efficacy, were based on very limited data. For the safety of Tdap in pregnant women, because the company did not include pregnant women in the prelicensure study, the ACIP reviewed safety data from pregnancy registries, the Vaccine Adverse Event Reporting System (VAERS), and other small studies with subjects numbering 100 or fewer. The determination of efficacy was based on the existing knowledge of transplacental maternal antibodies. The recommendation made based on biological

plausibility instead of clinical trial is unusual. The case point demonstrated that, when the problem stream (high infant deaths) and viable policy alternative (policy stream) converge, the traditional framework requirements, even the most crucial ones (safety and efficacy), could give way.

#### 5.4. A Case Study of Malaysia's HPV Immunization Program

The HPV vaccine was licensed in Malaysia in 2007. The country launched a national immunization program in July 2010. Within two years, the program achieved its target of vaccinating around 250,000 13-year-old schoolgirls annually. Reasons for presenting this case study include: *First*, the time between the vaccine was licensed in Malaysia, which allowed access to the private market, to a fully operational national program that achieved population access was 5 years, which is shorter compared to other national programs. *Second*, the HPV vaccine introduction in Malaysia is a school-based approach. Takeda's dengue vaccine (TDV) does not have clinical data for concomitant administration with other vaccines in the existing national programs. From a market access point of view, it would be cost-saving to introduce TDV in a captured environment where targeted vaccines, the students, would gather daily. The alternative to the school-based program would be clinic-based, which would result in extra visits, giving burden to parents and the health system. Saidatul Buang and colleagues described the processes and lessons learned through the lens of Kingdon's framework (Buang, Ja' Afar, Pathmanathan, & Saint, 2018). This case study is based on the paper and interviews with key government officials involved in the establishment of the program.

#### **The Initiation**

In response to World Health Assembly's resolution in 2005 (WHA58.22) (WHO, 2005), the Ministry of Health in Malaysia convened an expert committee in 2006 to evaluate the evidence pertaining to the HPV immunization program. A policy proposal for a national HPV immunization program was submitted to the Ministry's policy committee.

### **The Kingdom's Framework:**

**Problem stream:** Academic institutions generate evidence of cervical cancer epidemiology, circulating HPV serotype epidemiology, and the status of health expenditure for cervical cancers. The pharmaceutical industry's participation in the problem stream remained in evidence generation through sponsorship of health economic studies or conferences that raised the awareness for benefits of the immunization. Two papers that described the local burden of cervical cancer were believed to play a crucial role in changing the opinion toward the HPV immunization program (Aljunid, Zafar, Saperi, & Amrizal, 2010).

**Policy stream:** the ministry of health convened a group of experts to review HPV immunization programs in Australia, the United Kingdom, and other countries. MoH used the evidence to gather support from the Ministry of Finance, Ministry of Education, and Ministry of Women (Sharifa & Aljunid, 2010).

**Political stream and the Policy Window:** The cancer-related death of the Prime Minister's wife was used to convey the need for the vaccine via the media. The prime minister chaired the cabinet. It was considered a policy window when the Ministry of Health presented a cabinet paper to the recently bereaved Prime Minister to propose a national HPV immunization program. The prime minister approved the policy and budget, moving the program forward.

**Policy Entrepreneur:** The ministry of Health played a crucial role in initiating the proposal, sustaining the momentum before the final endorsement of the Prime Minister that facilitated, and concretized the program. It seemed less evident that the pharmaceutical companies played any role as a policy entrepreneur. The pharmaceutical companies' involvements that were recorded in the paper did not exceed the conventional ones, which include: flexibility in pricing, evidence generation, conference sponsorship, and support for implementation, i.e., cold chain and distribution logistics support.

#### 5.5. A Toolkit Questionnaire for Political Economy Analysis on Dengue Vaccine

- **Problem Stream:**
  - **Credible Indicators:**
    - How was the burden of dengue infection epidemic reported in the target country?
    - How were these reports conveyed to the key stakeholders?
  - **Focusing Events:**
    - How do outbreaks or mortality cases of dengue and the related reports draw the public's attention?
    - How would the above events affect the decisions taken during the strategic planning cycle of the Ministry of Health?
  - **Issue Framing:**
    - How was the dengue fever epidemic in the country described/framed by the media?

- Has the issue been framed, or perceived as a disease that touches certain targeted populations?
  - How was the reported burden perceived by different stakeholders, including the people in general, the private sectors, and the political leaders?
  - Would the framing of the dengue fever epidemic by foreign media affect foreigners' decision-making when it comes to choosing the country as a destination for tourism?
- **Policy Stream:**
  - **Policy Community Cohesion:**
    - How would you describe the circle of technocrats/academics that influence the vaccine policy of the country? (Is the circle small? What kind of value do they adopt? Were they divided in their opinions? If yes, what could be the major conflicts of ideas about dengue fever epidemic control?)
  - **Guiding Policy Institution:**
    - What is the leading academic institute on infectious disease control, particularly for dengue in the country? How is it organized? Who is the leader of the institute?
    - What is the leading governmental institute on the same issue? How well does this institute conduct intersectoral coordination to promote a policy?
    - How do the above institutions converge on issues of the vaccine?
  - **Viable Policy Alternatives:**
    - How do the local epidemiology of dengue and policy environment contribute to the promotion of the option of single-dose TDV for outbreak response?

- How do the guiding policy institutions apply the Integrated Vector Management (IVM) for dengue control (WHO, 2012c)? Describe the country's current strategy and priorities for dengue control.
    - Would Wolbachia infected mosquito be adopted as one of the alternative policies for dengue control?
  - **Policy Entrepreneurs:**
    - Based on the country's history of adopted public vaccines, for example, HPV vaccine, was there an identifiable "policy entrepreneur" from the policy community circle that could bridge the gap between technocrats and bureaucrats and develop a policy that is feasible and implementable?
- **Politics Stream:**
  - **Political Transitions:**
    - Is political continuity in place to assure sustained commitment to access to the vaccine?
    - Is there any potential transition of political administration that could open a policy window?
    - How do the campaigns and subsequent elections affect the politicians as to making promises to combat dengue epidemics?
  - **Hidden Alliances:**
    - Could any group or individual's personal experience as a dengue patient, or their experience dealing with infected family members be leveraged to form policy alliance?

- Are there any key decision-makers of vaccine policy who have first-hand experience with the disease?
- **Political ideology**
  - Does nationalism or protectionism play a role in influencing the public vaccine decision?
- **Policy Advocates and Interest Group Mobilization:**
  - How would the relevant NGOs/Civil societies, or other professional societies, such as the Pediatrician Society or the Internal Medicine Society, champion the issue of dengue and advocate for a public dengue vaccine?
  - How would the above groups influence the public's perceptions of vaccine and address vaccine hesitancy?
- **External/Global Influences:**
  - How would development partners or international institutes, such as WHO, World Bank, JICA, GAVI play a role in influencing the NIP profile?

## 5.6. Example Questions by Categories of Interviewees

Categories of Interviewee	Preference Weighting	Example Questions to the Category
ACIP member		
	Yes	Describe the principle of public vaccine prioritation, or SOP?
		How would a new vaccine's discussion be initiated?
		What analytical framework you used?
		Look back to history, were there instance when dispute over a certain vaccine was heated?
		Describe the impacts of the different stakehodlers on your decision making: medicla society, anti-vaccine movement..
		How are the impacts of the external stakeholders, like WHO SAGE, USCDC ACIP?
DG of Health, City government(non-dengue endemic)		
	Yes	What do you think is unique about the local public vaccine programs?
		Describe how the additional public vaccines that are differnet than the central government's ones.
		Describe the process through which the decisions were taken for the additional public vaccine?
		How bipartisanship, local council, media, perception of risk, finance and dramatic events affect the local vaccine policy?
DG of Helath, City government (dengue endemic)		
	Yes	Described the most recent epidemic of dengue?
		And how does your team prepare to prevent the next outbreak?
		You opnion on vaccination against dengue locally?
Journalists		
	Yes	Please review the past major events on infectious disease epidemics.
		What are the factors that would affect the decision to include a story of outbreak?
		Using the H1N1 in 2009 for example, how do you think the media coverage shaped the public's opinon on the risk of the disease, and the vaccine?
		The anti-vaccine movemnet is less impactful in Taiwan, comparing to our neighboring countries, like Japan. How do you explain this, from the media's perspective?
Anti-vaccine movement leader		
	Yes	Describe the formation and major focus of advocacy of your organization?
		Tell me stories of the vaccine victims and their perspectives.
		How do you describe the impact of your organization on the public vaccine policy?
Chair of medical society		
	Yes	How does your society form public vaccine opinion or make recommendations?
Cinicains		
	Yes	Your experience and perceptions on the implementation of Taiwan's public vaccine policy.
Vector control experts (entomologists)		
	Yes	Decribe the evolution of the vector control policy of Taiwan along with the dengue outbreaks.
Frontline disease control officers		
	Yes	How do you describe the overall strategies of the disease control strategy in the 2014-2015 dengue outbreaks in Taiwan?
Former Ministry of Health higher level officials		
	Yes	How did the dynamic in public vaccine discussion led to our vaccine industry policy?
		Describe the process of the establishment of Taiwan's HPV immunization program.

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