

Introduction of pentavalent vaccine in Indonesia: a policy analysis

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Abstract

The introduction of pentavalent vaccine containing *Haemophilus influenzae* type b antigen in Indonesia's National Immunization Program occurred nearly three decades after the vaccine was first available in the United States and 16 years after Indonesia added hepatitis B vaccine into the program. In this study, we analyzed the process that led to the decision to introduce pentavalent vaccine in Indonesia. Using process tracing and case comparison, we used qualitative data gathered through interviews with key informants and data extracted from written sources to identify four distinct but interrelated processes that were involved in the decision making: (a) pentavalent vaccine use policy process, (b) financing process, (c) domestic vaccine development process and (d) political process. We hypothesized that each process is associated with four necessary conditions that are jointly sufficient for the successful introduction of pentavalent vaccine in Indonesia, namely (a) an evidence-based vaccine use recommendation, (b) sufficient domestic financing capacity, (c) sufficient domestic vaccine manufacturing capacity and (d) political support for introduction. This analysis of four processes that led to the decision to introduce a new vaccine in Indonesia may help policy makers and other stakeholders understand and manage activities that can accelerate vaccine introduction in the future.

Key words: Necessary condition, new vaccine introduction, pentavalent vaccine, process tracing, sufficient condition

Key Messages

- The decision to introduce a new vaccine is a complex process that often deviates from guidelines and generalizations, therefore country-specific knowledge of the process is required to enhance the possibility of future new vaccine introduction.
- Evidence building, financing, vaccine manufacturing and politics are separate but interdependent processes that lead to the decision to introduce a new vaccine.

Introduction

The introduction of new vaccines in lower income countries usually lags behind that in higher income countries. Previous studies have demonstrated factors that are associated with a higher probability of accelerated introduction. For example, higher probability of introduction correlates with country per-capita gross domestic product,

vaccine cost, immunization program strength, disease burden, disease treatment cost, access to external funding and the political and institutional capacity to decide and implement the introduction (Gauri and Khalegian 2002, Miller and Flanders 2000). Accelerated introduction of *Haemophilus influenzae* type b (Hib) vaccine was correlated with democratic institutions, introduction by neighboring

countries and eligibility for funding from Gavi, the Vaccine Alliance (Gavi) formerly the Global Alliance for Vaccines and Immunization, whereas an increase in vaccine price, financing uncertainty, and being situated in East Asia, Pacific, Europe and Central Asia contributed to delayed introduction (Shearer *et al.* 2010).

Although frameworks to assist decision makers for introducing new vaccines are available (Burchett *et al.* 2012b; Erickson *et al.* 2005; World Health Organization 2014b), there are evidence that the decision making process in practice is more complex and does not always follow these guidelines (Burchett *et al.* 2012a; de Oliveira *et al.* 2013). A more thorough within country assessment can highlight the complex and diverse process of new vaccine introduction across countries. For example, domestic vaccine production was an important driver for the introduction of hepatitis B vaccine in Taiwan but not in Thailand, whereas vaccine price was important in Thailand but not in Taiwan (Munira and Fritzen 2007). Understanding the processes and drivers of the introduction of new vaccines within countries is important for accelerating future introductions (Gauri and Khalegian 2002; Munira and Fritzen 2007).

Indonesia introduced Hib-containing pentavalent vaccine in its National Immunization Program (NIP) in 2013, 16 years after introducing hepatitis B vaccine in 1997 (Yulitasari 2014). As described elsewhere (Mahoney 2004; Muraskin 1995), the introduction of hepatitis B vaccine was highly influenced by the involvement of the International Task Force on Hepatitis B Immunization. The Task Force's vaccine introduction model demonstrated that success was attributable to strong high-level political support, development of appropriate delivery policies through large-scale demonstration project, availability of adequate supply of affordable vaccine, and sustainable financing. The model was successfully replicated in several other countries and led to the integration of Hepatitis B vaccine in the Expanded Program for Immunization and a push to establish a global fund for its financing.

In the intervening period between the two vaccine introductions, major political reforms occurred in Indonesia following the 1998 economic crisis—including the transition from an authoritarian regime to a democratic state, an increase in local government autonomy, and a move to decentralize the health system. Hence, the introduction of the pentavalent vaccine in 2013 offers an opportunity to examine the current process of vaccine introduction in Indonesia in this new political context.

This study explores the process through which the decision to introduce the pentavalent vaccine in Indonesia was made. We supplemented the pentavalent vaccine introduction case with other cases where new vaccines were proposed to be introduced to postulate hypotheses of necessary and sufficient conditions for successful vaccine introduction. Findings from this study may help policy makers focus on those factors that may accelerate future vaccine introduction in Indonesia.

Methods

We used process tracing to explore the processes and conditions leading to successful vaccine introduction in the cases of pentavalent and other vaccines in Indonesia. We sought to identify whether the presence of certain conditions was necessary and sufficient for a successful introduction.

Case study selection

Following WHO, we defined new vaccine introduction as the addition of a new vaccine or vaccine formulation into the national immunization program (World Health Organization 2014b). As such,

the pentavalent introduction was identified as the only successful case in Indonesia in recent years. Additionally, we identified plans and processes to introduce Japanese encephalitis B (JE), the pandemic H1N1 flu, rotavirus and inactivated poliovirus (IPV) vaccines that did not or had not yet resulted in successful introduction.

Data collection

We conducted in-depth interviews between June and October of 2013 with 13 individuals knowledgeable about the process of pentavalent vaccine introduction in Indonesia, selected based on their relevant positions in organizations known to have influenced the process (Richards 1996). An interview guide was used and included questions exploring the process of vaccine introduction, actors and organizations that were involved in the process, and contexts considered to be important or influential throughout the process.

Interviews took on average 60 minutes, were conducted in English or Bahasa Indonesia, and were transcribed from the recordings or, in cases where interviewees denied recording, from interview notes. All interviews were conducted by first author. Written documentation, such as regulations, presentations made by relevant officials, newspaper articles and peer-reviewed papers were also obtained to corroborate and complement claims made during the interviews.

Analysis

Interview transcripts were used as our main data source to identify the intervening processes that resulted in the introduction of the pentavalent vaccine (Tansey 2007). We systematically identified factors that potentially determined the outcome of pentavalent and other vaccine introduction in Indonesia by following a policy analysis framework (Buse *et al.* 2005; Walt and Gilson 1994). Specifically, we used this policy analysis framework in a thematic analysis to predefined categories (Table 1) into which specific codes emerged from the interview transcripts and written sources would be assigned (Gale *et al.* 2013). We subsequently identified and organized sufficiently distinct information within each category as subcategories (Buse *et al.* 2005), and pieced together the vaccine introduction decision making process and preconditions by applying process tracing (George and Bennett 2005). Finally, we constructed hypotheses of necessary conditions using available information from other vaccine introduction plans (Goertz and Levy 2007). Coding of the interview transcripts and written documentations were done in OpenCode 4.02 (ICT Services and System Development and Division of Epidemiology and Global Health 2013).

Table 1. Operational definition of coding categories

| Coding category | Definition |
|-------------------|---|
| Policy content | Policy's substance, i.e. introduction of new vaccines into Indonesia's national immunization program |
| Policy actors | Individuals or organizations, domestic or international, who influence the policy process |
| Policy process | The course of action from the initiation to implementation of a policy |
| Political process | The interaction characterized by negotiation and conflicts among actors during the policy process, or process resulted from the prevailing political system |
| Policy context | Variables that influence the policy process but reside outside of the policy process itself |

Ethics

Required ethical approvals were obtained from Harvard T.H. Chan School of Public Health, USA (protocol #IRB13-0379), and Padjadjaran University Faculty of Medicine, Indonesia (protocol #233/UN6.C2.1.2/KEPK/PN/2013).

Results

Interviewees consisted of former and current mid-to-top level officials from the WHO, Program for Appropriate Technology in Health (PATH), and the Indonesian Ministry of Health, as well as from the Indonesian Technical Advisory Group on Immunization (ITAGI), Indonesian House of Representatives and PT Bio Farma (Table 2). An official from UNICEF Indonesia was invited but was unable to participate because of conflicting schedule. An invitation was sent to a private vaccine manufacturer representative office in Jakarta, but no response was received.

We identified four separate but interdependent processes occurring between 1998 and 2013 that affected the decision to introduce the vaccine. Those processes were: the pentavalent vaccine use policy, vaccine financing, domestic vaccine production and political processes (Table 3).

Pentavalent vaccine use policy process

The first process involved an official government recommendation to use the new vaccine. The formal process to include the pentavalent vaccine in the NIP began in 2007 with a recommendation from the newly established ITAGI for its use in the NIP (Hadinegoro *et al.* 2011). This took place one year after WHO revised its recommendation to introduce Hib vaccine globally regardless of demonstrated disease burden (World Health Organization 2006). Prior to this revision, WHO recommended the introduction of Hib vaccines for the prevention of pneumonia and meningitis among children under-5 years of age (World Health Organization 1998), focusing on countries with demonstrated disease burden. However, local evidence of Hib disease burden was not demonstrated until a vaccine-probe randomized control trial in Lombok, Indonesia, was concluded in 2002 (Gessner *et al.* 2005). The 1998 WHO recommendation was followed by the Indonesian Pediatric Society that included Hib vaccine in their immunization schedule (Indonesian Pediatric Society

Task Force on Immunization 2000), but the government did not yet issue any specific consideration about its use in the NIP.

Taking into account cold chain capacity and vaccine wastage, ITAGI's recommendation was updated in 2008 with a suggestion to produce the vaccine domestically as a liquid pentavalent vaccine, and was updated twice in 2010 adding recommendations for immunization scheduling (Indonesian Technical Advisory Group on Immunization 2010). In the same year, the Ministry of Health included the plan to introduce pentavalent vaccine in 2013 in its Comprehensive Multi-Year Plan (CMYP) for years 2010–2014. The Ministry of Health passed a ministerial decree in June 2013 to introduce the pentavalent vaccine. Taking into account PT Bio Farma's capacity to produce the vaccine in sufficient amount and the preparedness of the NIP to deliver the new vaccine, the new NIP was rolled out in four provinces in August 2013 and planned to be expanded to cover all 34 provinces within a 1-year period.

Pentavalent vaccine financing process

The second process involved assured financing for the new vaccine. Pentavalent vaccine introduction in Indonesia was supported by Gavi. The request for Gavi funding was proposed in 2011 and was approved in 2013, with Gavi cofinancing amounts for the years 2013–2016 of (in million US\$) 9.2, 12.7, 21.4 and 7.8, respectively, whereas the Indonesian government contributions for the same years were proposed to be (in million US\$) 1.9, 9.9, 19.8 and 28.3, respectively. According to one interviewee, the government capacity to finance vaccine introduction at the time was insufficient so that it required a higher Gavi contribution and a partial reallocation of the government's fuel subsidy to make the introduction possible (Interviewee-13 [I-13]), and that otherwise the introduction would not have occurred (I-2).

Funding for routine immunization programs came from Indonesia's annual national budget such that the availability of government financing funds was also subjected to the government's budgeting process (I-13). The proposed pentavalent introduction financing had to be approved within the Ministry of Health, and then by the National Development Planning Bureau and be subjected to negotiation with the Ministry of Finance before finally being discussed with the parliament and passed as a bill (Ministry of

Table 2. Interviewees and institutions represented

| Institution | Number of interviewees | Consideration |
|--|------------------------|---|
| Sub-Directorate of Immunization—The Ministry of Health (MoH) | 2 | Responsible for the design and operation of national immunization program in Indonesia |
| World Health Organization, Indonesia | 2 | Indonesia's NIP largely followed WHO recommendations. WHO provides technical support for the Ministry of Health |
| PT Bio Farma | 2 | A government-owned vaccine manufacturer that supplied all vaccines used in the NIP |
| The Indonesian Technical Advisory Group on Immunization | 1 | The national immunization technical advisory group for Indonesia, mandated to provide vaccine-related advice to the Ministry of Health |
| The People's Representative Council (parliament) | 1 | Parliament's approval is needed for vaccine introduction budget |
| Provincial level health office—West Java Province | 1 | Provincial and city/district level health office, as an organ of local governments, were responsible to fund the operational costs of immunization program. In addition, local government can also recommend their own vaccination practices in addition to the NIP |
| City level health office—city of Bandung, West Java | 2 | Same as above |
| Independent consultants | 2 | The individuals had worked with PATH in Indonesia and had extensive experience with Hep B and Hib pilot projects |

Table 3. Key events leading to pentavalent introduction in Indonesia

| Year | Policy process | Financing process | Vaccine production process |
|------|--|-------------------------|---|
| 1998 | First WHO recommendation | | Technology transfer agreement between PT Bio Farma and the Netherlands |
| 2002 | Lombok Hib study commenced | | Hib clinical lot produced by PT Bio Farma |
| 2003 | | | Clinical trials started |
| 2005 | Lombok study results published | | |
| 2006 | Second WHO recommendation | | |
| 2007 | First ITAGI recommendation | | |
| 2008 | Second ITAGI recommendation | | Liquid pentavalent vaccine production started |
| 2010 | Third ITAGI recommendation | | |
| | Introduction planned in CMYP 2010–2014 | | |
| 2011 | | GAVI application | |
| 2012 | | GAVI approval | Clinical trials ended |
| | | Central budget approval | |
| 2013 | Health Minister's decree | | PT Bio Farma pentavalent vaccine PentaBIO™ received approval from Indonesia's Food and Drug Administration agency |

Finance of the Republic of Indonesia 2014). Additionally, provincial and district level governments had to contribute to finance the operational cost of the immunization program (Health Minister of Republic of Indonesia Decree 2013a). However, because the pentavalent vaccine only added an antigen to the tetravalent vaccine already included in the NIP, it did not impose additional operational costs to local governments.

In addition to the availability of funding for introducing a new vaccine, the Ministry of Health considered sustainability of funding to be an important consideration prior to making a decision to introduce a new vaccine (I-4). Even though the Ministry of Health had allocated immunization program financing within a routine expenditure category, which in theory would guarantee funding availability, the program had experienced funding cuts. Sustainability of the immunization program was considered important to maintain public trust and hence the continued successful delivery of immunization services.

Pentavalent vaccine domestic production process

The third process addressed the existence of a domestic producer for the new vaccine. PT Bio Farma is a government-owned company and is the only local vaccine manufacturer in Indonesia. PT Bio Farma's technical capacity to manufacture Hib vaccine, initially in freeze-dried preparation, was obtained through a technology transfer agreement started in 1998 with the National Institute for Public Health and the Environment, from the Netherlands (Beurret *et al.* 2012). In response to ITAGI's recommendation, however, PT Bio Farma initiated a new technology transfer to produce liquid, Hib-containing, pentavalent vaccine in five-dose vials. Clinical trials were completed in 2012 and soon after the vaccine received the national regulatory authority's approval for use. PT Bio Farma's pentavalent production capacity was sufficient to fulfill 20% of the national demand in 2013, and 100% in 2014 (Politik Indonesia 2012). One interviewee considered the lengthy process for acquiring the capability to produce the vaccine as one of the key rate limiting factors for introducing the pentavalent vaccine (I-6); but once PT Bio Farma was able to produce the vaccine there was a need to purchase and use the product (I-4).

Political process

The fourth process involved political discussion and actions within government bodies. The political process of pentavalent vaccine

introduction was embedded within the existing technical and bureaucratic processes inside the Ministry of Health and between the Ministry of Health and other stakeholders. Within the Ministry of Health, the immunization program had to compete with other priorities and eventually would need to gain support from the Health Minister (I-4). The importance of the Minister's political ideology in shaping the official decision is best illustrated by way of an example. During the H5N1 avian flu outbreak, 2005–2009, the then-Health Minister of Indonesia used anti-Western sentiment in the country with the largest Muslim population in the world (Lakoff 2010) and introduced the concept of 'viral sovereignty' that prevented Indonesia from sharing its circulating strain of H5N1 with the global health community (Supari 2008). The rejection of JE vaccine use, described later in this article, also occurred within the same Ministry of Health leadership for allegedly similar anti-foreign sentiment (I-2, I-3). By contrast, her successor, a Harvard graduate and accomplished researcher at the Ministry of Health, was described as more open to global collaboration (Sciortino 2012).

The Indonesian parliament also played an important political role in the review of government budgets, especially with its authority to examine the proposed ministry's budget line-by-line in the in-depth review process, during which it was not uncommon for the parliament to deny or postpone the approval of a budget line (I-2, I-5, I-13). In addition, health system decentralization that occurred in Indonesia since 2001 was acknowledged to have weakened Indonesia's immunization program (Directorate General for Disease Control and Environmental Health 2011).

Advocacy was considered important to secure political support from the parliament through regular consultation meetings between the Ministry of Health and the parliament (I-2). In addition to the Ministry of Health, WHO also played a role in advocating pentavalent vaccine introduction. Two parliament members were sent to join a group of policy makers in the Sabin Vaccine Institute's Sustainable Immunization Financing Program in Senegal, August 5–6, 2013, to learn about positive experiences with pentavalent vaccine introduction in other countries. This had a positive impact on generating political support for pentavalent introduction in Indonesia (Berita Satu Online 2013). Of note, the issue of pentavalent vaccine introduction seemed to have circulated within a closed network of policy makers, unlike the ongoing immunization program that could produce a wide public discussion and to some

extent rejection, especially with regard to possible use of certain porcine elements that would make the vaccine impermissible by Islamic law. Regardless, the Ministry of Health and PT Bio Farma acted cautiously and were in close consultation with the Council of Indonesian Ulama (Majelis Ulama Indonesia) to assure support from the largest ulama representation body in Indonesia (I-4, I-10, I-13).

The view that a domestically manufactured vaccine was necessary for the introduction was expressed strongly by two of the interviewees (I-3, I-4). Procuring vaccines from PT Bio Farma provided economic advantages compared to importing vaccines (I-13), such that purchasing vaccines from PT Bio Farma was considered as a good investment and would prevent national reserves from going abroad (I-8, I-9). This view is in line with Indonesia's commitment to achieving self-sufficiency not only for vaccine production but also in economic development in a more general sense.

Processes observed with other vaccines

We briefly looked at four cases of unsuccessful vaccine introduction in Indonesia, to see the role of the four processes described above.

Japanese encephalitis vaccine

Although Japanese encephalitis infections have been identified in Indonesia since 1972, evidence supporting a new vaccination policy was not available until results of a 2-year hospital-based surveillance in Bali were published in April of 2006 (Kari *et al.* 2006). Presentation of the evidence in a meeting organized by the International Vaccine Institute in September 2006 resulted in a strong support by the Ministry of Health to introduce JE vaccine in Bali as soon as possible. Subsequently, an action plan for routine and catch-up vaccination of Balinese children using live attenuated vaccine from China was developed in February 2007 (International Vaccine Institute 2007). ITAGI followed up with a recommendation on the use of JE vaccine in a pilot study in Bali in 2008 (Hadinegoro *et al.* 2011). A Chinese JE vaccine available at a very low cost (approximately US\$0.20/dose) was planned to be used in Indonesia through PATH's JE Program (International Vaccine Institute 2009). However, the introduction plan was reportedly rejected by the Health Minister, because the minister did not want to use an imported vaccine in the NIP (I-3).

The case demonstrated the failure to introduce a new vaccine due to the absence of several necessary conditions, mainly political support. In the presence of evidence supporting the use of JE vaccine, we argue that this lack of support stemmed from the lack of domestic production capacity. Financing process, on the other hand, was not initiated or was terminated very early as a result of the political decision not to introduce the vaccine.

Influenza pandemic vaccine

WHO declared H1N1 influenza a pandemic in June 2009 and called for the full use of global influenza vaccine production capacity to produce the pandemic vaccine (Chan 2009). Shortly thereafter WHO called for assistance for least-developed countries to cope with the pandemic, resulting in a total of 122.5 million doses of donated vaccine globally (World Health Organization 2012). Although Indonesia was eligible to receive WHO donated pandemic vaccine, Indonesia did not make the request (World Health Organization 2011). Local news media reported that the parliament urged the Ministry of Health to refuse the donation because of the possibility of virus strain mismatch (Republika Online 2010). Meanwhile, the Ministry of Health was concerned that the short-

term nature of pandemic vaccine delivery would create mistrust for the nation's entire immunization program, once the influenza program was discontinued (I-4).

Similar to JE introduction, this case demonstrates the necessity of having political support to introduce a new vaccine and underlines the involvement of the parliament in the process. Arguably, evidence of a pandemic should have sufficed to support the local use of H1N1 pandemic vaccine, in spite of the parliament's concern. Further, as the vaccines were donated, a large part of funding for the program should have been addressed. It is not unlikely that the parliament's objection was politically motivated and may have resulted from (as well as reinforced by) the Ministry of Health's main concern, i.e. the lack of guaranteed supply of vaccine due to the unavailability of locally produced vaccine.

Rotavirus vaccine

Rotavirus infection had been demonstrated to account for 60% of hospitalized childhood diarrhea cases in Indonesia (Soenarto *et al.* 1981). Physicians from Gadjah Mada University in Indonesia had been studying rotavirus infection in children since late 1970s and were actively engaged to accelerate the introduction of rotavirus vaccine in Indonesia. In 2013, they started the manufacturing process of a low cost rotavirus vaccine at PT Bio Farma in collaboration with Murdoch Children's Research Institute in Australia (Murdoch Childrens Research Institute 2013). Domestically produced vaccine was considered necessary to reduce costs and therefore increase the possibility of introduction (I-1). PT Bio Farma's rotavirus vaccine is estimated to be ready in 2016 (Antarnews.Com 2011), which could then result in the decision to introduce the new vaccine into Indonesia's NIP.

In this case, the introduction of rotavirus vaccine was still very early in its process. Although very limited information was available regarding the process, the presence of avid advocates who were keeping the process moving was readily observable. It could be argued that the process thus far—from research to technology transfer—was taken based on insights that having PT Bio Farma produce the vaccine would increase the likelihood of getting other processes, politics and financing, moving toward supporting rotavirus vaccine introduction.

Polio IPV

In 2002, WHO offered Indonesia the opportunity to conduct a study to evaluate the possibility of switching to inactivated polio vaccine from oral polio vaccine that had been used in Indonesia's NIP since 1982 (Gendrowahyuhono *et al.* 2010). Switching to IPV was suggested as part of the global polio eradication strategy by WHO to maintain a high level of population immunity against polio in light of possible circulating vaccine derived polio viruses from the oral form. Following a recommendation from the Indonesian acute flaccid paralysis expert group, a pilot study was conducted in the city of Yogyakarta starting from year 2007 and was planned to be finished in 2011 using an imported vaccine. Funding for the pilot came mostly from WHO (Health Minister of Republic of Indonesia Decree 2007). At about the same time, in 2007, PT Bio Farma started a technology transfer process for IPV production with the Japanese government (Gendrowahyuhono *et al.* 2010) and was expected to be ready to produce its own IPV by 2016 (Pt Bio Farma 2012). Because of favorable results from the switch, the Ministry of Health decided to continue the use of IPV in Yogyakarta beyond the pilot study using the imported vaccine, financed from the central

and local government budget (Health Minister of Republic of Indonesia Decree 2013b).

Unlike the other cases above, the polio IPV immunization program was using imported vaccine financed by the government. However, this case is different from the other cases, in that the IPV immunization program was a pilot conducted in one province. This case shows that the government could agree on introducing an imported vaccine in a certain program.

Hypothesized conditions for successful vaccine introduction in Indonesia

We hypothesize that the processes described above are associated with certain conditions that are necessary for new vaccine introduction in Indonesia.

Hypothesis #1: an official evidence-based recommendation is a necessary condition for introduction

By the addition of Hib, the Indonesian NIP has included 8 of the 12 antigens recommended by WHO for routine immunization in all countries. The included ones are the BCG, DPT-Hepatitis B-Hib, polio and measles vaccines, while the remaining four are rotavirus, pneumococcal, rubella and HPV vaccines. The Ministry of Health included in its 2010–2014 Comprehensive Multi-Year Plan the plan to introduce or to prepare for the introduction of JE, pneumococcal and typhoid vaccines and to have ITAGI actively review evidence to introduce rotavirus and influenza vaccines (Directorate General for Disease Control and Environmental Health 2011). So far, vaccines outside of WHO recommendations have never been introduced in the NIP. However, even though WHO recommendations have been the starting point of new vaccine introduction in Indonesia, availability of some supporting evidence of local disease burden and vaccine cost-effectiveness are necessary prior to introduction. This can be demonstrated by the Lombok study prior to Hib vaccine introduction, and studies being done in preparation for the introduction of other vaccines such as JE surveillance study in Bali, and studies for supporting the use of rotavirus and IPV vaccines. Local evidence is necessary for policy makers to design appropriate vaccination scheduling and targeting and more importantly to justify new vaccine introduction amidst competing priorities. Evidence from neighboring countries or from countries with similar characteristics to Indonesia does not suffice to justify new vaccine introduction, as demonstrated by the case of pandemic flu vaccine introduction. In this case, even though it was evident that the novel H1N1 flu virus was circulating worldwide, the vaccine was rejected because of the absence of local evidence supporting its use. In addition, this recommendation includes other considerations such as cold chain capacity, preferred vaccine presentation, and vaccination schedule.

Hypothesis #2: Sufficient domestic financing to pay for the delivery of a new vaccine is a necessary condition for introduction

At full scale, the introduction of pentavalent vaccine into Indonesia's NIP requires an additional US\$30 million in annual NIP financing, or a 15% increase from the pre-introduction budget. Even though the immunization program budget is allocated in the Ministry of Health's routine spending budget (I-5), funding cuts had happened and the immunization program had experienced vaccine shortage due to lack of funding (I-4). Unlike the ongoing

immunization program, however, there is no guarantee that funding will be made available for introducing new vaccines.

It is evident that Indonesia had problems allocating sufficient funding for the introduction of pentavalent vaccine and it would not have happened without Gavi support and the serendipitous availability of funding from Indonesia's gas subsidy cut. The increase in global gasoline prices that occurred at the time forced the government to gradually reduce the gas subsidy and reallocate the funding to social programs, among others to finance pentavalent vaccine introduction. Although immunization program financing can come from both domestic and donor funding sources (Health Minister of Republic of Indonesia Decree 2013a), Indonesia has been self-financing its routine immunization program. Traditionally, more than 50% of NIP financing comes from the central government budget, about 40% came from provincial and district government budget and less than 10% comes from external sourcing like Gavi (Directorate General for Disease Control and Environmental Health 2011). Even though Gavi's co-financing was critical for the introduction of the pentavalent vaccine, domestic funding sources were required by Gavi and needed to continue beyond the 4 year Gavi co-financing agreement. Moreover, as Indonesia's economic condition has improved, it is graduating from Gavi and will not be eligible for future funding to support new vaccine introduction. Hence, although alternative external funding sources can be available for future vaccine introduction, it is probably a good idea to ensure that domestic funding sources will be available and not to rely on external funding sources, as it is generally very hard for countries like Indonesia to project and predict their availability (McQuestion *et al.* 2011).

Hypothesis #3: Demonstrating national production capacity for a new vaccine is a necessary condition for introduction

For Indonesia, the ability of PT Bio Farma to produce the vaccine of interest is necessary for introduction. To date, every vaccine used in Indonesia's NIP is manufactured by PT Bio Farma, whose 'commitment was to develop national vaccine industry's independence, such that the government is not required to import vaccines to fulfill national needs' (Bachtiar and Nurlaela 2014). The attempts to introduce the H1N1 and JE vaccines illustrate how the lack of national production capacity for vaccines can prevent introduction. Further, even though available evidence supported the use of rotavirus vaccine in Indonesia, there was no plan to introduce the rotavirus vaccine into the NIP by using an imported vaccine and instead a technology transfer program was initiated to prepare for the introduction.

The push to use nationally produced vaccines in the NIP can be traced back to post-colonial Indonesia. Dr. Sardjito, the first Indonesian to head PT Bio Farma in the post-independence era (1945 – 1946), already aimed at self-sufficiency in vaccines against measles and cholera as one of the ways to achieve President Soekarno's economic ideology of *berdikari* (acronym from *berdiri di atas kaki sendiri*, or 'standing on its own two feet') (Neelakantan 2015). In the late 1970s, Indonesia opposed Singapore's intention to take on the role as ASEAN's Hepatitis B vaccine production center, fearing that this plan would undermine Indonesia's aim to be vaccine self-sufficient (Anwar 1994). More recently, PT Bio Farma established a National Vaccine Research Forum comprised of academic researchers, the government, and PT Bio Farma itself. The Forum drafted a vaccine research roadmap with vaccine self-sufficiency as one of its core goals (The Jakarta Post 2011). Hence,

even though an imported vaccine was used in the IPV vaccination program in Yogyakarta, it is very likely that IPV use will not be expanded in the NIP until PT Bio Farma is ready to fulfill the need.

Hypothesis #4: Political support is a necessary condition for new vaccine introduction

The failures to introduce the pandemic flu and JE vaccines provide two examples of political obstacles to new vaccine introduction in Indonesia, resulting from actions taken by the parliament and by the Health Minister, respectively. Indonesia's past experience with hepatitis B vaccine also demonstrates the importance of political support for vaccine introduction (Mahoney 2004; Muraskin 1995). The death of a close friend of President Soeharto due to liver cancer was an important factor in his decision to push for the addition of hepatitis B vaccine to the NIP and its early expansion to cover the whole country.

Considering that vaccination is one of the most cost-effective, life-saving public health interventions available, introducing a new vaccine that has sufficient evidence about effectiveness and safety should receive support from rational decision makers. The two cases of the JE vaccine and pandemic flu vaccine, however, demonstrate that political motives such as economic sovereignty and nationalism can influence the decision to introduce a new vaccine. Arguably, decision makers involved in new vaccine introduction can have different motives and the end result will depend on whether a consensus could be reached. While decision to introduce and accelerate the use of a new vaccine in the past could be made by an authoritative figure such as former President Soeharto, such a figure may not exist in a democratized, decentralized and multi-party system, as in Indonesia today (Aspinall and Fealy 2003). In the case of the pentavalent vaccine, the decision to introduce this new vaccine gained needed political support because potential opposition was probably eliminated, or at least reduced, by the appointment of a new health minister and/or by the fact that a domestically produced vaccine was going to be used.

Hypothesis #5: the four conditions are jointly sufficient for introduction

Finally, we hypothesize that the decision to introduce a new vaccine will occur if all four aforementioned conditions were simultaneously present. The case of the pentavalent vaccine introduction supports this hypothesis. Following vaccine availability, the first condition to be met was the issuance of recommendations by the WHO and ITAGI, supported by evidence from Lombok. Domestic production of vaccine was initiated about the same time, although a domestic vaccine product was not available for use until just before the introduction. In the meantime, the Ministry of Health maintained political support from within its own organization and with outside political bodies, and secured funding from both the government and donor. By contrast, the absence of one or more of these necessary conditions was observed in the failed attempts to introduce the JE, rotavirus and H1N1 vaccines in Indonesia.

Discussion

In this study, we utilized the case of pentavalent vaccine as an example of a successful new vaccine introduction in Indonesia, and we analyzed the processes that led to the decision to introduce the vaccine. Our analysis of key actor interviews and written sources demonstrates that the decision making process for introducing a new vaccine in Indonesia involves four separate but interdependent

processes, namely, new vaccine use policy, financing, national production and political processes. Further, using information from other vaccine introduction attempts, we postulate that these processes are associated with four necessary conditions for introduction, namely, an evidence-based recommendation for new vaccine use, sufficient national financing capacity, sufficient domestic vaccine production and political support for introduction. We further hypothesize that the presence of all four necessary conditions is sufficient for successful introduction of a new vaccine.

Previous studies have demonstrated the complexity of the process leading to successful new vaccine introduction, with similarities and differences between countries (Burchett *et al.* 2012a; Chen 2013; Gupta *et al.* 2012; Munira and Fritzen 2007; Udin *et al.* 2013). While guidelines for introducing new vaccines and multi-country studies can provide general insights on this process, they do not sufficiently explain this complexity. For example, WHO's New Vaccine Introduction guideline explains at length the importance of evidence supporting the introduction of new vaccines and the strength of the health system (World Health Organization 2014a), but neglects the importance of politics and domestic vaccine production that we find important in our study. In addition, even though studies employing quantitative methods such as regression analyses are valuable to infer which factors affect the probability and the timing of introduction, they cannot say which factors are necessary or sufficient for the introduction to occur. Our study serves to fill these gaps, for the case of Indonesia, and provides an alternative perspective on the decision making processes to introduce a new vaccine.

WHO recommendations and guidelines for vaccine use, based on evidence of disease burden, vaccine characteristics, and programmatic strength, typically inform government decisions to introduce a new vaccine (Burchett *et al.* 2012a). Similarly, we found that the Indonesian Ministry of Health regards scientific evidence as a crucial consideration in the decision to introduce a new vaccine. In that regard, WHO recommendations usually act as a prompt (Mantel and Wang 2012) for the decision making process to be initiated, supported by domestic scientific recommendations from technical policy groups such as ITAGI (Health Minister of Republic of Indonesia Decree 2010). However, we found no written guidelines or frameworks that explain how the government should weigh and use this evidence, or how ITAGI ought to aggregate and rank evidence. ITAGI's role is also limited to advising the Ministry of Health and thus the recommendation may or may not be followed. Hence, while some scientific evidence supporting the introduction of a new vaccine is necessary, it is not clear what kind of evidence is sufficient to move government's decision toward introducing a new vaccine. This seems to be the case in general (Mantel and Wang 2012). For example, even results from a randomized controlled trial (RCT) were subject for debate and did not seem to accelerate introduction of Hib vaccine in Indonesia. For a country whose 248 million people consists of more than 300 ethnic groups inhabiting more than 900 islands it is understandable that the generalizability of locally acquired evidence to the whole country, such as that from the Lombok Hib study (Gessner *et al.* 2005), can be a subject of debate. Arguably, the validity of RCTs can be threatened by effect modification in different populations and availability of more supporting evidence is desirable (Victora *et al.* 2004). It may be the case that evidence from research studies must be supplemented by other types of information, including implicit knowledge possessed by those making the decision (Nutley *et al.* 2003).

Indonesia's government expenditure for immunization programs was predicted to grow from \$138.8 million in 2009 to \$219.6

million in 2014, but funds from central and local governments were expected to decrease over time (Directorate General for Disease Control and Environmental Health 2011). Cuts in immunization program financing may result in temporary shortages, causing temporary disruption in scheduled immunization, and thus reduction in immunization coverage that can result in an upsurge of vaccine-preventable diseases (Hinman *et al.* 2006). The impact of funding cuts on immunization coverage was observed during the financial crisis that started in 1997, when routine government health spending dropped by 10 and 28% for the years 1997–1998 and 1998–1999, respectively, accompanied by a 25% point decline in DPT3 immunization coverage (Simms and Rowson 2003). More recently, a temporary shortage of IPV vaccines during the transition from WHO to government funding was a cause of public concern and reported in the media (AntaraneWS.Com 2013). Thus, the decision to include national immunization program financing in the routine part of the Ministry of Health spending budget through legislation was a move in the right direction to sustain and stabilize the program's delivery, as has been shown by the experience in the Americas (Andrus *et al.* 2011). However, this applies only to ongoing immunizations and does not include the cost of introducing new vaccines. Thus, the availability of local funding for new vaccine introduction is subject to more uncertainties.

Previous studies found that domestic vaccine production can enhance the possibility of vaccine introduction in Indonesia (Mahoney 2004), as well as in other vaccine producing countries (Milstien *et al.* 2007). Our study further suggested that domestic vaccine production may even be *necessary* before a vaccine is introduced into the NIP. In addition to economic justifications (World Health Organization 2014a), we found other reasons for using a nationally produced vaccine include health system capacity support, in the form of vaccine delivery to provinces and maintenance of cold chain, and political reasons to reduce dependency on imported vaccines. Although the Ministry of Health uses imported vaccines, such as the use of IPV vaccine for a demonstration project in Yogyakarta and the use of meningococcal vaccine for Muslims going on pilgrimage to Mecca, these can be considered as special cases outside of the routine immunization program and the use of imported vaccines might not have occurred otherwise.

At least two issues affected the decision to use imported meningococcal vaccine instead of waiting for a domestic vaccine to be produced. First, meningococcal vaccination was made obligatory by the Saudi Arabian government for all Muslims going on Hajj pilgrim to Mecca. With approximately 300 000 Indonesian going for Hajj every year, public unease would occur if these pilgrims were unable to perform the Hajj because of the government's non-compliance with the regulation. Secondly, the cost of the vaccine was fully borne by the pilgrims; and the vaccine cost would be a small fraction of the Hajj cost. In the case of IPV, the program was still at its pilot stage. Hence, the vaccine need was much smaller than for those vaccines rolled out at full scale, and the pilot was considered necessary for establishing evidence to support future use of IPV in the NIP.

It has been previously recognized that the new vaccine introduction process is a political process involving a multitude of actors with differing power and interests (Gauri and Khalegian 2002; Wonodi *et al.* 2012). In the Ministry of Health, the Sub-Directorate of Immunization is particularly responsible for keeping the introduction process moving forward, but its role is limited to the process of generating the policy for new vaccine use in the NIP, and the decision making process must take into account the roles and interests of other players. In the financing process, the Ministry of Health must work with the Ministry of Finance, the parliament and Gavi or

other donors on the final decision about funds. The capacity to domestically produce a vaccine lies in PT Bio Farma, a government-owned corporation under the supervision of the Ministry of State Owned Enterprises.

Arguably, the health minister plays the most decisive political role in new vaccine introduction. Even in countries where national immunization technical advisory groups operate, the final decision to introduce a new vaccine often becomes a political decision made by the health minister (McQuestion *et al.* 2011), as also demonstrated in the case of JE vaccine introduction in Indonesia. However, as a political process the decision to introduce a new vaccine is prone to interventions from other political figures or groups, especially those with substantial influence such as the International Task Force on Hepatitis B Immunization and former President Soeharto in the case of hepatitis B introduction (Muraskin 1995), or the parliament in the case of the pandemic flu vaccine introduction, and in some cases from donor agencies (Mantel and Wang 2012). Our study did not reveal any strong and prominent figure advocating or opposed to the introduction of pentavalent vaccine, suggesting that prominent advocate or policy entrepreneur is not necessary for introduction, although its presence may be helpful to accelerate the process.

A major limitation of our study is that it focused on only one successful new vaccine introduction and readers are advised that generalization to other contexts must be done with caution. This is especially true for the importance of domestic vaccine production capacity, which is non-existent in most countries, especially in low to middle income countries. Even for countries with domestic vaccine manufacturing capacity, its importance to the decision to introduce a new vaccine must be viewed within the larger political and economic contexts (Munira and Fritzen 2007). Limited information was available on other vaccine introduction cases, so that analyses with similar rigor to the pentavalent vaccine case were not possible. This is likely due to recall bias because of the recency of pentavalent vaccine introduction, because of the relatively small scale of other vaccine introduction, or because the process was terminated or incomplete. Although interviewees were individuals highly familiar with NIP decision making process in Indonesia, our study lacks comprehensive representation from decision makers at regional and global levels and therefore does not capture the roles of these contexts on Indonesia's national decision making process. It is also possible that the same outcome could be achieved through processes different from those identified by our study. In addition, the limited number of cases does not allow us to weigh the relative importance of each condition in different contexts. For example, in the presence of a strong political push for introduction, the relative importance of evidence may be reduced, and vice versa.

Nonetheless, we expect that the framework developed here can be useful to assess the progress of vaccine introduction in Indonesia and to identify actions that can be taken to accelerate the progress of vaccine introduction. Our findings suggest that accelerating the introduction of new vaccines can be achieved by initiating the four processes and ensuring that every necessary condition is met in the shortest time possible. Fostering research studies to gather more evidence supporting the use of the vaccine, facilitating early or faster technology transfer and development, guaranteeing new vaccine introduction funding through legislation, and identifying political champions for vaccination program are among ways that may accelerate new vaccine introduction in Indonesia.

Conflict of interest statement. None declared.

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