

Dengue Vaccine Research Challenges Toward Independency of Vaccine Seed in Indonesia

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ABSTRACT

Dengue infection control is one of the main priority health programs in Indonesia. Although the vector control has been implemented, the dengue fever outbreak cannot be prevented. Hence, another preventive approach, such as dengue vaccination needs to be carried out. To accelerate towards independency of vaccine seed, the dengue vaccine research and development is conducted in form of consortium for synergized research. Objective: The study aims to identify challenges in the research process of developing dengue vaccine in Indonesia. Methods: The challenges of developing dengue vaccine research for each stage was identified and grouped based on the criteria management and technical challenges. Results: In Indonesia, the dengue vaccine is being developed in a tetravalent recombinant sub unit protein form, utilizing a porcine free (halal) production system and using Indonesia's virus strains. The development process involves the universities, research institutes, vaccine industry and government. However, this innovative and laboratory based research still faces challenges, in terms of the imported reagent procurement system, less flexible financial scheme, unequal laboratory standard for each member consortium, heavy workload, and also limited experience and knowledge for bioprocess technology. Endeavors have been done to overcome these challenges, specifically, building the trust among the members, having the same vision, sharing the access, facilities, and technology. However, to accelerate vaccine product, sustainable and specific mechanism of finance, secure reagents availability, sufficient infrastructure and staff competency improvement for long-term research are required.

Keywords: *dengue vaccine, challenge, research*

1. INTRODUCTION

Dengue infection control is one of the main priority programs and the second target of the Ministry of Health of the Republic of Indonesia Strategic Plan 2015-2019 [1]. Dengue virus has four distinct serotypes and these serotypes circulate throughout Indonesia [2], [3]. The efforts to control dengue vector have been carried out, however, it is still difficult to prevent the dengue fever outbreak. Therefore, another preventive action, such as, vaccination, is considered fundamental. On the other hand, the currently released dengue vaccine has shown less promising result, either in terms of efficacy and safety, particularly to the seronegative population [4], [5]. This indicates there is still a demand for dengue vaccine research and development. The dengue vaccine research and development is conducted in Indonesia to answer the demand. It is also one of the product oriented innovative research supported by the Indonesia's government because it conforms to the national development agenda.

The President of Republic of Indonesia has released a national development agenda consists of nine development priorities called Nawa Cita, in which, the seventh is to accomplish economic autonomy by promoting the domestic economy strategic sectors. One of which is implemented through the President Instruction Number 6 in 2016 about the acceleration of pharmaceutical and medical device industry development [6], [7]. This instruction is further developed into the action plan of pharmaceutical industry and medical device development through Ministry of Health Regulation No. 17 of 2017 in the course of basic material autonomy and to increase pharmaceutical and medical device industry competitiveness [8].

The dengue vaccine research and development in Indonesia is implemented as a consortium in order to synergize the research, to avoid duplication and to increase the budget efficiency, and eventually, to accelerate the production of vaccine seed. The dengue vaccine consortium involved 9 institutions, representing the ABG sectors; academic such as research institute and university (A), business (B), and

government (G). Since 2013, the dengue vaccine consortium was established and coordinated by the government representative; Centre for Research and Development of Biomedical and Basic Health Technology, The National Institute of Health Research and Development (Puslitbang Biomedis dan Teknologi dasar Kesehatan, Balitbangkes). The academic consortium members were universities, including, Faculty of Medicine University of Indonesia (FM UI), Faculty of Medicine University of Gadjah Mada (FM UGM), Faculty of Medicine University of Airlangga (FM Unair), Primate Animal Study Center, Bogor Agricultural University (PSSP IPB) and research institutes, including, Eijkman Institute of Molecular Biology, Agency for the Assessment and Application of Technology (BPPT) and Indonesian Institute of Science (LIPI). The business consortium member was PT Biofarma. The exploration of potential vaccine and adjuvant feasible to be developed was conducted since 2013 to 2014, followed with the evaluation to accelerate the product development. Since 2015, the dengue vaccine consortium resolved to focus on the development of recombinant sub unit protein based vaccine using strains circulating in Indonesia and in halal (porcine free) system. At the same year, the consortium members changed to be 7 institutes, namely, NIHRD, FM UI, FM UGM, LBM Eijkman, BPPT, PSSP IPB and PT Biofarma.

2. METHOD

The research collaboration involved seven institutions where each member was responsible for the development of one particular dengue virus serotype and their task division was based on their specific expertise. The consortium developed the dengue vaccine in the form of a tetravalent recombinant sub unit protein, utilizing a porcine free (halal) production system and using Indonesia's virus strains. Then, the challenges of developing dengue vaccine research for each stage was identified and grouped based on the criteria management and technical challenges. The consortium members and relevant management team were routinely assembled to evaluate the research progress.

3. RESULTS AND DISCUSSION

The research area division of each institution member is shown in Table 1. Each has specific responsibilities based on their expertise, capability, and research facility. PT Biofarma, as the assigned manufacturer of the expected product, provides technical assistance in every step of the research in order to ensure the outcome can be applied and commercialized by the industry sector.

Table 1. The Research Area Division In The Dengue Vaccine Consortium

No.	Research Area	Institutions
1	Vaccine development for dengue serotype 1 and genotype I	Puslitbang Biomedis dan Teknologi dasar Kesehatan, Balitbangkes Consortium coordinator
2	Vaccine development for dengue serotype 1 and genotype IV	FK UGM
3	Vaccine development for dengue serotype 2	FK UI
4	Vaccine development for dengue serotype 3	BPPT
5	Vaccine development for dengue serotype 4	LBM Eijkman
6	Cultivation in the fermentor and purification Adjuvant Formulation Vaccination in animal model Technical assistance for every research phase	PT Biofarma
7	Immunogenicity test and efficacy test in non human primate model	PSSP IPB

The virus gene characterization result from isolated dengue vaccine strain indicated that DENV-1 genotype I and genotype IV, DENV-2 Cosmopolitan genotype, DENV-3 genotype I and DENV-4 genotype II were the most dominant strains circulating in Indonesia [2].

The routine meeting of the consortium members to evaluate the research progress identified many challenges in relation to acceleration towards production. The challenges were varied. One of them was the reagent availability. Most of the reagents used in the experiments had to be imported and the procurement system was complex and time-consuming. The procurement system was carried out centrally for 7 institutions through a review process by a technical team to evaluate the suitability of research reagent need. The time needed for the evaluation of the technical team is around 1-2 weeks. Then the procurement team conducted an auction process or other procedures in accordance with applicable regulations. If the procurement procedure is smooth, the time needed from the auction process to the determination of the tender winner was around one month. Sometimes, tender failures occur because there were no companies interested in bidding. Possibly because the types of reagents are quite a lot with the quantity of each reagent are few and the time for contract completion is short. While there are some reagents that require more time for the import process. So that the auction process was repeated, which finally takes a long time. The e-catalog process was carried out to speed up the availability of reagents. But there are still many research reagents that are not available in the e-catalog list. If there is

an e-catalog list, sometimes the amount needed is insufficient. If the procurement process takes 1-2 months, then the contract completion period requires 3 months, so the reagents needed will be fully available in the researchers around 4-6 months. This is a significant challenge for innovative laboratory-based research.

Furthermore, the budget management mechanism was less flexible to accommodate the dynamic of the innovative multi-year research. The laboratory infrastructure condition of each institute was not the same. There were limitations of laboratory infrastructure. Some institutions were responsible for developing vaccines according to dengue virus serotypes, but due to limited laboratory equipment, so the completion time was delayed for all four dengue serotypes. Some of the research process was continued to other institutions that have more complete laboratory equipment.

There were also challenges in terms of human resources. Although the human resources were considerably competent in their field, they have other responsibilities which sometimes distract their focus from the consortium activities. In addition, the recent experiment result indicated the need of expertise in bioprocess technology, while currently, there is very limited number of expert in such field available in the country. These challenges postponed the expected output. As a result, depicted in Figure 1, the dengue vaccine roadmap schedule was delayed. For example, the previously supposedly a one year study became 2 or 3 years study.

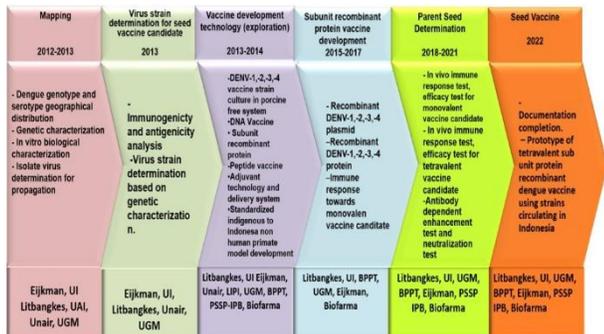


Figure 1. The Dengue Vaccine Consortium Roadmap

Indeed, the vaccine research and development requires a significant amount of time from the exploratory phase until it becomes commercially available product (Figure 2). Thus, specific strategies should be applied in order to achieve the expected result. The dengue vaccine consortium roadmap was the strategies developed to achieve product output based on this vaccine development pipeline.

There are some considerations of dengue vaccine research and development being conducted in the form of consortium. It is aimed to achieve the national vaccine production independency, particularly, a seed vaccine that is produced in a halal (porcine free) system, developed using virus strains

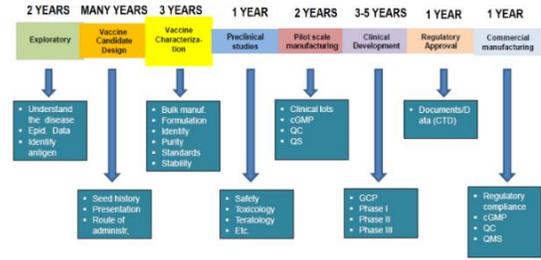


Figure 2. Vaccine Development Pipeline

From four serotypes predominantly circulating in Indonesia. The seed vaccine has to be safe for the environment in a sense of not introducing new virus variant into the environment. The technology platform should be the one that is already developed by the industry and can be performed by research institutes using an efficient and cheap production system. Based on these considerations, the consortium decided to focus on the development of sub unit protein recombinant using a halal (porcine free) production system.

To build a collaborative research in the form of consortium, some conditions are needed such as having the same vision, which is the national vaccine seed independence and for the national benefit, to improve the people's health status. It also requires trust among the researchers where each members contributes their competency. Moreover, the management support is equally essential. This includes providing competent human resources, continuous multi-year research funding provision, and sufficient structure and infrastructure.

Before being handed over from the consortium to the industry, the parental seed vaccine has to fulfill the standards of recombinant product required by the WHO TRS no. 814 Annex 3 in 1991 [9]. The standards include complete documentation of the expression vector and host cells, the genetic stability, sequences of the cloned gene and the expression process. In addition to the WHO standards, there is another standard required by the industry. The product should be consistent, safe, effective, high yield and high recovery process. Another highlighted limitation faced by the consortium are the lack of experts in the bioprocess field and analysis methods need to be established. While it is possible to do collaboration with the foreign institutions, the legal documentation and material transfer agreement (MTA) arrangement requires a significant amount of time.

To overcome the ongoing challenges, there are crucial things to be improved. A special reagent procurement mechanism, sustainable budget and more flexible budget management which accommodate the sustainability of the innovative research in Indonesia are required. There should be enough qualified human resources available to be responsible for a reasonable workload so they are able to focus on conducting the innovative research. Furthermore, the mechanism of legal

process for each consortium member should be simplified. These managerial aspects should be resolved in order to sustain the collaboration and the research team can focus more on the research substance.

4. CONCLUSION

The challenge faced by the consortium technically was it must meet the requirements of recombinant product vaccine seed standards according to WHO TRS 814 A3, 1991, also in research management (imported reagent procurement system, less flexible financial scheme, unequal laboratory standard and heavy workload of researcher). Not only technical, the managerial support is necessary to overcome the challenges. Taking everything into account, an innovative research with product output demands adequate amount of competent human resources, sustainable budget, special mechanism for reagent procurement and budget management, and simplified legal collaboration procedures.

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