Appendix 3

Grant-in aid for Health, Labour and Welfare Administration Promotion Survey Project
(Special Research Project for Health, Labour Sciences)
Research Reports

Biostatistical Perspective to Accelerate the Planning of Clinical Trials in Vaccine Development

Shared Research: Research on Clinical Trial Planning and Design and Information Used to Evaluate the Efficacy of Vaccines for Approval in Japan

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Abstract:

Thirty-nine vaccines have been approved since the inception of PMDA until March 31, 2022, while 59 studies have been evaluated in review reports to determine their efficacy. The number of approved vaccines in Japan increased due to policy recommendations and interest in infectious diseases after the Japanese government issued the "Vaccine Industry Vision" in 2007. Nevertheless, it fell when vaccine safety concerns became a social issue, and no vaccine of domestic origin has been approved since 2016.

An analysis of the indications and clinical trial designs of vaccine products approved in Japan revealed that domestic-origin vaccine development companies had not made sufficient progress against new diseases. Moreover, it became apparent that companies developing vaccines of domestic origin have no experience in conducting large-scale clinical trials evaluating the efficacy outcomes based on the clinical endpoint, nor experience conducting multi-regional clinical trials, nor studies in other countries.

In contrast, there are signs of change in the vaccine development landscape in Japan currently. There is a gradual shift from catching up to closing the vaccine gap to participating in multi-regional clinical trials conducted by global pharmaceutical companies for simultaneous worldwide development and clinical trials to evaluate efficacy based on clinical evaluation endpoints.

According to the WHO Guidance on Clinical Evaluation of Vaccines[5)], vaccine efficacy is generally evaluated based on the clinical event onset of infectious diseases after vaccination. Thus, conducting clinical trials evaluating efficacy based on clinical endpoints is considered essential in the future for developing vaccines against new diseases, particularly for domestic companies.

Owing to the circumstances in the clinical trial environment in Japan, which may be challenging to conduct such trials, intervention by the government may be a viable option in establishing an international platform for multi-regional clinical trials and combined analyses.

A. Objective

The coronavirus infectious disease pandemic has had a significant impact from various perspectives worldwide. The development of new vaccines in various countries has been moving at a breakneck pace due to the magnitude of the impact of the infection, with the enormous resources of industry, government, and academia.

The Japanese government also called for rapid vaccine development. It actively supported the development of domestic new coronavirus vaccines by investing heavily[3)] in policy packages included in the "Strategy for Strengthening Vaccine Development and Production Systems" [2)], which the Cabinet approved on June 1, 2021[1)]. This was captured in the supplementary budget of 2020. Simultaneously, despite such research and development budgets being spent, no domestic vaccines were made available for practical use in Japan as of the end of March 2022. This fact highlighted the existence of various issues in the development system for vaccines in Japan,

One of the challenges in vaccine development in Japan is the lack of a system to design clinical trials and plan them under unexpected circumstances rapidly.

Therefore, by summarizing and analyzing the information on the development of approved vaccines to date, this study aimed to clarify issues and points to consider when developing vaccines for new diseases, including vaccines used during pandemics.

We specifically collected information on how the efficacy of commercialized vaccines was evaluated during the approval review in Japan. This is based on the information on the package insert information service web page (https://www.pmda.go.jp/PmdaSearch/iyakuSearch/) of the Pharmaceuticals and Medical Devices Agency (PMDA). In addition, we summarized and analyzed the clinical trial planning and design, information used for efficacy evaluation, development period, differences in development between domestic and other countries, and approval background, and discussed points to consider in developing future vaccines for new diseases.

B. Methods

We collected the review reports for vaccines that were newly approved (defined as new active ingredient-containing drugs in the “Application for Product Approval” [Notification No. 1121-2] of the Pharmaceutical and Food Safety Bureau of November 21, 2014) and published on the package insert information service web page, https://www.pmda.go.jp/PmdaSearch/iyakuSearch/. In total, there were 39 newly approved vaccines from April 1, 2004, when the PMDA was established, to March 31, 2022 (including five vaccines sharing clinical trials with other drugs, for reasons such as a single product with multiple names). We confirmed that the review policies in the "Outline of Review" section of the clinical data were checked in each review report. In addition, we selected 63 studies used in the efficacy evaluation review and then extracted 59 studies excluding duplicates.

The following information was provided for

each vaccine product: brand name, ingredient name, approval applicant, indication, and classification of the review (eligibility for a review for special approval or preferential review, such as that for orphan drugs). Other information provided includes the approval date, whether the post-market efficacy assessment (including immunogenicity assessment) was requested in the approval condition or Risk Management Plan (RMP), and the classification of the origin of the development of the active ingredient (herein, in which the domestic company developed the active ingredient is referred to as domestic origin vaccine, and the foreign company developed the active ingredient is referred to as foreign origin vaccine). We also summarized the distinction between companies with domestic- and foreign investment that applied for approval.

The following data were collected and summarized for a clinical trial: vaccines used in the trial for approval, whether it was a confirmatory clinical trial or not (such as an exploratory trial), study designs, control drugs used, and types of control drugs (placebo [adjuvant-only, saline, etc.], drugs at various doses, other vaccines [same efficacy or no indication regarding the purpose]), number of participants in the full analysis set, number of participants in the test group, region of the clinical trial (global multi-regional clinical trials including Japan, domestic only, foreign only, etc.), adaptive designs (including the plan to change the number of participants enrolled or dose selection of the active drug group during the study that can be confirmed from the review report), the primary endpoint, secondary endpoints described in the review report, and study implementation period. In addition, the use of characterized designs and analyses (Bayesian statistical, combined analysis and cluster randomized clinical trials) were summarized. According to the Guidance on Adaptive Design Clinical Trials for Drugs and Biologics of the U.S. Food and Drug Administration (FDA) [4], adaptive design is defined as a clinical trial allowing prospectively planned modification based on data accumulated from clinical trial participants. It is a broad concept that includes discontinuing a trial based on an interim analysis, among other things. However, the adaptive elements in the trial design are not always described in the review reports. For example, suppose the approval in Japan is obtained long after the trial is completed. In that case, whether an interim analysis was conducted is not always specified in the review report. Therefore, we focused on changes in the number of participants enrolled or the dose selection in the active treatment group, which are thought to have a significant impact on the period of vaccine development and would be explicitly described in the review reports.

By cross tabulating the extracted data, we attempted to characterize the size of clinical trials conducted during vaccine approval in Japan, trial design, and differences due to domestic and foreign development.

Further, if efficacy or immunogenicity was evaluated in an individual trial in the review report for which the combined analysis results

were submitted as review documents, the results were summarized for each trial. However, if efficacy was evaluated only in the combined analysis results, the combined analysis results were treated as a single study.

(Ethical considerations)
No ethical considerations were required because this study was an investigation of a previously published review report.

C. Study conclusion

(1) Principal developers of vaccines in Japan (Table 1, Figure 1)

Domestic companies released > 50% (21 products: 53.8%) of the vaccines into the market. This indicates domestic companies are developing many vaccines. However, when the active ingredients of vaccines developed by domestic and foreign companies were compared, domestic vaccines accounted for 14 out of 39 products (35.9%). The proportion reversed when foreign vaccines were excluded.

Following the announcement of the Vaccine Industry Vision (2007), the emergence of the A/H1N1 influenza pandemic (2009), and the Middle East respiratory syndrome (MERS) outbreak (2012), the number of approved vaccines gradually increased during the period following the launch of industry promotion measures by the government and rising social concern about the infectious disease crisis. It peaked at six yearly in 2013. Nevertheless, the number of approved vaccines gradually decreased after 2013. An active HPV vaccination campaign was halted that year, and people expressed concerns about vaccine safety. Furthermore, domestic vaccines have not been approved since 2016. This was when the "Vaccine and Blood Products Industry Task Force" was formed in response to the issue of a specific company illegally manufacturing blood products, among other things. Moreover, when the application for approval of a cell culture seasonal influenza vaccine developed by a domestic company was withdrawn in 2017, the number of approved vaccines for domestic- and foreign-origin vaccines fell to zero. Only one foreign-origin vaccine was approved yearly until the COVID-19 epidemic in 2020, following which approval was granted to several new coronavirus vaccines in 2021.

(2) Overview of Clinical Trials Utilized for Efficacy Evaluation

a) Size of the clinical trial and development entities (Figure 2, Figure 3, Table 2)

The average number of participants in the vaccine efficacy trials was 7,480.3, with a median of 423 (first quartile: 216; third quartile: 4277.5). The number of cases analyzed in 16 of 59 trials (22.0%) exceeded 3,000 participants, which is the sample size for safety evaluation exemplified in the WHO Guidance on Clinical Evaluation of Vaccines[5]. The clinical study with the most participants included in the analysis was the 006 study of RotaTeq Oral Solution, which had 67,935 participants. This number was not used to assess efficacy; however, it was for detecting patients with intussusception. In the 10PN-PD-DIT-043 study of Synflorix aqueous

suspension intramuscular injection, the largest sample size analyzed for efficacy was 45,977.

A cross-tabulation of clinical trial size based on vaccine development origin, domestic or foreign, showed that no domestic-origin vaccine clinical trial included more than 1,000 patients. The KIBPCI-A-J302 study conducted to develop Adsorbed Cell-Cultured Influenza Vaccine H5N1 Intramuscular Injection, "Kitasato Daiichi Sankyo," of 60 μg/mL and 30 μg/mL had the most patients included in the analysis for domestic-origin vaccines, with 794 patients.

b) Study size and the primary endpoint

(Figures 4, Table3)

Except for the two studies with RotaTeq Oral Solution for Japanese patients, immunological endpoints were used as the primary efficacy endpoints in the 39 clinical trials (66.1%) with less than 1,000 patients for analysis. Twenty trials (33.9%) with 1,000 or more participants were analyzed, except for two trials, where a clinical endpoint (clinical event) was used as the primary efficacy endpoint, resulting in 18 studies (90.0%). The 810705 study for the approval of cell culture influenza vaccine H5N1 "Takeda" and the same vaccines approved to Baxter and Study Q-Pan-002 submitted for the approval of Alepanrix (H1N1) intramuscular injection were the two trials that were excluded.

No clinical trials using clinical endpoint as the primary efficacy endpoint have been conducted in developing domestic vaccines. Except for small studies (less than 1,000 participants analyzed) and influenza vaccines, the efficacy of foreign-origin vaccines was primarily assessed using clinical endpoints.

c) Implementation status of multi-regional clinical trials

(Table 4)

Two vaccines (5.1%), Shingrix intramuscular injection and Silgard 9 aqueous suspension for Intramuscular Injection Syringes, which are foreign-origin vaccines, were confirmed and approved in multi-regional clinical trials with participants from Japan, and three corresponding clinical trials (5.1%).

All the clinical trials for the domestic-origin vaccine that were evaluated for efficacy were conducted in Japan. No clinical trials were conducted in foreign countries or as multi-regional clinical trials, including Japan.

d) Clinical trials with a distinctive design and analysis

The C4591001 study for Comirnaty intramuscular injection was the only one in which the primary endpoint was evaluated using the Bayesian statistical test.

Comirnaty intramuscular injection (C4591001 study), Silgard 9 aqueous suspension for Intramuscular Injection Syringes (Study 001), and RotaTeq oral solution (Study 006) were the agents that used adaptive design studies defined in "B. Methods" for the efficacy evaluation by PMDA. The specifics of the trial plan that needed to be modified differed. For example, in the case of Comirnaty intramuscular injection, the dose was chosen when the trial progressed from Phase I to Phase II/III. In

addition, the number of participants to be included in the safety evaluation or the RotaTeq oral solution was chosen.

A cluster-randomized, double-blind study was used in the regulatory review of Synflorix aqueous suspension intramuscular injection (OOBPD-DIT-043 study). It was also used to evaluate an Ebola vaccine (Merck's Ervebo, approved in the U.S. and Europe) [6], though this is not in the scope of this study.

Clinical trials for Vaxzevria intramuscular injection (COV001, COV002, COV003, and COV005 studies) and Gardasil aqueous suspension for intramuscular injection syringes (007, 013, and 015 studies) were conducted using the combined analysis. However, the drugs were handled differently during the review process. Vaxzevria intramuscular injection, a novel coronavirus vaccine, was not assessed separately for each study, but the combined analysis was used to determine efficacy in the special approval. The efficacy of Gardasil was verified with the results of individual studies in the review, and the confirmation of the efficacy evaluation using the combined analysis was addressed in a supplemental manner.

D. Discussion

(1) Current status of clinical development of vaccines in Japan obtained from this study

The Japanese government issued the "Vaccine Industry Vision[7]" in 2017. It stated that the vaccine industry in Japan is dominated by small and medium-sized enterprises (companies with < 1,000 employees and business revenues of < 10 billion yen), except for Takeda Pharmaceutical Co., Ltd. Furthermore, three of the four influenza vaccine manufacturers, accounting for most vaccine sales, were foundations or incorporated associations at the time. Therefore, it was noted that the scale of R&D differs significantly from that of foreign pharmaceutical companies involved in the vaccine business, which increasingly became consolidated worldwide. For example, the R&D investment of the U.S. vaccine industry is more than ten times that of Japanese vaccine manufacturing companies.

“Vaccine Industry Vision" also pointed out that no new vaccine has been approved since the last hepatitis A vaccine was developed in the 1990s and that Japan lacks seeds for developing new vaccines.

Further, other issues the vaccine industry should address include maintaining the same development capability level as general therapeutic agents other than vaccines. This is especially essential for development capability that will enable quick response to future social demands for vaccine efficacy and safety based on international clinical development and regulatory standards and the clinical development capability to conduct large-scale clinical trials.

In addition, the "Report of the General Conference on Countermeasures against H1N1 Influenza (A/H1N1), "[8] which summarizes the countermeasures against the 2009 A/H1N1 influenza pandemic, recommends that vaccine manufacturers are supported, and production systems should be strengthened. This is

necessary while encouraging the development of cell culture and intranasal vaccines to ensure citizens are vaccinated as quickly as possible from a national security standpoint.

We reviewed the "Strategy for Strengthening the Vaccine Development and Production System" approved by the Cabinet on June 1, 2021, which was prepared after the outbreak of the new coronavirus, to see how these policy recommendations have shifted and how the various points raised in previous policy recommendations have been improved. The document includes new elements not previously included in vaccine-related policy documents, such as venture support, vaccine development in new modalities, monitoring system enhancement, a pharmaceutical approval process to allow for emergency use, and establishing a dual-use manufacturing system. However, 14 years after the " Vaccine Industry Vision, the reality that Phase III trials are challenging to conduct and a lack of international development experience remain unresolved. "

According to the review of vaccine approvals in this study, the development of domestic vaccines that were newly approved after the establishment of the PMDA was limited to the development of a combination of existing vaccines or modification of culture technology. This includes the 2005 rubella-measles vaccine, 2009 cell culture-based Japanese encephalitis vaccine, 2013-14 H5N1 novel influenza vaccine, and prototype pandemic influenza vaccines (including those derived from cell culture), which have not resulted in the approval of vaccines to prevent new diseases that require efficacy evaluation based on clinical endpoints.

However, the fact that domestic vaccines have not been approved since 2015 does not mean that vaccine development in Japan has not stopped. On December 16, 2013[9], the Ministry of Health, Labor, and Welfare requested a five-in-one vaccine (DTaP/IPV/HIB) from the industry association of vaccine development companies. In April 2022, two domestic companies submitted applications for approval[10][11]. In addition, domestic companies are currently developing intranasal influenza vaccines, which were expected to be developed according to the "Report of the General Conference on Countermeasures against Pandemic Influenza (A/H1N1)," using clinical trials to evaluate efficacy based on clinical events[12][13]. Other vaccines in development, such as malaria[14] and norovirus vaccines[15], have reached the clinical trial stage. In addition, the Coalition for Pandemic Preparedness Innovation (CEPI), a public-private partnership that aimed at promoting vaccine development, announced in a press release that it would provide $31 million in support for phase I and II clinical trials of a Nipah virus vaccine at the Institute of Medical Science, University of Tokyo[16].

However, all confirmative clinical trials for 5-in-1 vaccines are designed to evaluate immunogenicity[17][18]. Clinical trials for all development products other than intranasal influenza vaccines will be conducted in foreign countries in collaboration with foreign groups. Nonetheless, this does not rule out the

possibility that vaccine development, especially for new diseases, is being conducted overseas due to challenges in conducting verifiable clinical trials to evaluate the efficacy of vaccines based on clinical events in Japan.

Furthermore, compared to other therapeutic agents, one of the characteristics of vaccine clinical trials developed in Japan is the small number of multi-regional clinical trial projects. However, the number of multi-regional clinical trials conducted in Japan has recently increased. For example, 440 (57.0%) of the 789 clinical trial plan notifications submitted to PMDA in fiscal 2021 were multi-regional clinical trials conducted in Japan[19]. However, only 3 (5.1%) of the 59 vaccine-related studies used in the approval review in Japan were conducted as multi-regional clinical trials including Japanese participants, and the two drugs were Singrix (Japan Vaccine Co., Ltd. (at that time)) and Sylgard (MSD). Moreover, there were no domestic-origin vaccines for which multi-regional clinical trials or foreign clinical trials were conducted, indicating that when developing vaccines, domestic companies conducted the main trials for evaluating efficacy only in Japan. There are various possible explanations for this result; nonetheless, it is undeniable that one of them is that the years covered by this survey were a period of catch-up for the so-called “vaccine gap” in Japanese society, during which vaccines commonly used overseas were unavailable in Japan.

(2) Clinical Development Landscape of Vaccines in Japan

In section (1), we stated that, to date, no efficacy evaluations based on clinical endpoints have been conducted in developing vaccines of domestic origin. However, we believe the situation is gradually improving.

Using a free word search with the term "vaccine," 24 trials were discovered when searching for "specified clinical trials," "sponsor initiated clinical trials," or "clinical trials for pharmaceutical application" registered in the Japan Registry of Clinical Trials (jRCT), which is a registry of clinical trials in Japan (confirmed as of April 10, 2022). Furthermore, we confirmed that four multi-regional clinical trials involving Japanese participants (all sponsored by foreign companies) were registered as trials with efficacy evaluation based on clinical endpoints planned as the primary endpoint (jRCT2051210096, jRCT2031210159, jRCT2031210109, and jRCT2031200167, all of which cover drugs or indications not approved as of March 31, 2022).

In addition, when we searched on the Clinical Research Information Portal (https://rctportal.niph.go.jp) provided by the National Institute of Public Health using the term "Vaccines," which corresponds to 631 of JAPIC Drug Efficacy Classification Codes, 95 trials were found (confirmed on 2020 April 10, 2020). Among these, two international clinical trials by foreign companies (JapicCTI-205346 and JapicCTI-163378) and the two domestic intranasal influenza vaccine trials described in the previous section were identified when searching for trials that included Japan as the study site and evaluated efficacy based on the

clinical endpoint.

The current investigation does not cover these clinical trials because they are not approved in Japan or are being conducted for other indications. However, it is gradually becoming more apparent that vaccines are being developed in Japan concurrently with other countries worldwide through multi-regional trials rather than simply introducing foreign-approved vaccines to Japan to close the vaccine gap and that domestic companies are now accumulating experience in clinical trials evaluating efficacy based on clinical endpoints.

Nevertheless, it is unclear whether such advances in clinical trials will continue to be made in the future. According to the Pharmaceutical Research and Manufacturers of America (PhRMA) and European Federation of Pharmaceutical Industries and Associations (EFPIA), industry organizations of foreign pharmaceutical companies, the issues of clinical trials in Japan are the slow response of sites implementing clinical trials and the low recruitment per site, and the inefficient monitoring and CRA requirement, necessitating a reasonable number of personnel. This is a disadvantage when conducting a clinical trial to evaluate efficacy based on clinical endpoints, which is required when evaluating efficacy against new diseases.

Under such conditions, one possible way to promote vaccine development in Japan was establishing a platform that can help developers design multi-regional clinical trials or combined analyses under normal circumstances. This is essentially the preparation of a template for clinical trial-related documents, including protocols for multi-regional clinical trials, the implementation of common electronic case report forms (eCRF) among medical institutions, and conducting clinical trials based on the premise that multiple medical institutions collaborate through the use of central data review committees of efficacy and data safety monitoring committees.

(3) Limitations of this study

This study had some limitations. First, it did not comprehensively cover all reviewed clinical trials. We did not tabulate clinical trials other than those used as primary studies for efficacy evaluation during the review process. Hence, some post-marketing clinical trials and trials conducted in Japan to confirm domestic and foreign efficacy differences were excluded from the scope of the study. Second, development for specific age groups, such as pediatric vaccine development and clinical trials in the early stages of development, are not included in the scope of this study. Therefore, it was impossible to analyze clinical trials conducted after approval to evaluate vaccine long-term efficacy, conduct a comprehensive analysis of the clinical trial design conducted in Japan, or identify issues related to clinical trials at an early stage of development.

Third, there were also significant limitations in collecting data on the start date of clinical trials. For clinical trials of drugs approved before 2013, information on trial timing was frequently masked in review reports. Therefore, we attempted to supplement the data with

information from the clinical trial database of JAPIC or the U.S. clinical trials registry site, clinicaltrials.gov; however, many trials, especially those conducted solely in Japan, were not registered, regardless of whether the development was domestic or foreign-funded. Fourth, for clinical trials related to a specific product, it was difficult to confirm the timing of clinical trials related to a specific product because the registry did not have trials that corresponded to the names of the clinical trials listed in the review reports. Due to the difficulties in obtaining sufficient information, it was challenging to analyze the time required to develop each drug.

Fifth, as for surveys of clinical research information portals or jRCTs in this report, some trials that met the criteria may be overlooked due to the difficulty of specifying detailed search conditions and the fact that registrants do not always provide sufficient information.

E. Conclusion

Thirty-nine vaccines have been approved since the inception of PMDA until March 31, 2022, while 59 clinical trials have been evaluated in review reports to assess efficacy. The number of approved vaccines in Japan increased at times following the 2007 "Vaccine Industry Vision" due to policy recommendations and interest in infectious diseases. However, it decreased as safety concerns became a social issue, and no domestically produced vaccines have been approved since 2016.

An analysis of the indications and clinical trial designs of vaccine products approved in Japan revealed that domestic-origin vaccine development companies had not made sufficient progress against new diseases. Moreover, it became apparent that companies developing domestic vaccines have no experience conducting large-scale clinical trials evaluating efficacy outcomes based on clinical endpoints, multi-regional clinical trials, or clinical trials conducted in other countries.

In contrast, there are signs of change in the vaccine development landscape in Japan. In addition to catching up to close the vaccine gap, global companies are gradually beginning to include participants from Japan in multi-regional clinical trials for simultaneous worldwide development and conducting clinical trials to evaluate efficacy based on clinical evaluation endpoints.

According to the WHO Guidance on Clinical Evaluation of Vaccines[5)], vaccine efficacy is generally evaluated based on clinical events after and in the future. In Japan, the ability to complete clinical trials in which efficacy evaluation is based on the clinical endpoint is essential for developing vaccines against new diseases. This is especially for domestic companies. However, due to the difficulties in conducting such trials in a clinical trial environment in Japan, the government may take the lead in establishing an international platform where multi-regional clinical trials and combined analyses can be designed, which may prove beneficial.

Acknowledgment: Dr. Yasuko Asahina, Deputy Review Director of the Vaccine Evaluation Department of the Pharmaceuticals and Medical Devices Agency (PMDA), participated in the research as a study member, and other members of the department provided ideas for analysis and other assistance.

Table 1. Classification based on the origin of vaccines, the manufacture, or the vaccine development

	Classification by the origin of the manufacture	Classification by the origin of vaccine development
Domestic company	21 (53.8%)	14 (35.9%)
Foreign company	18 (46.2%)	25 (64.1%)

Figure 1. Number of approved vaccines by domestic and foreign origin of development and the social condition regarding vaccines in Japan

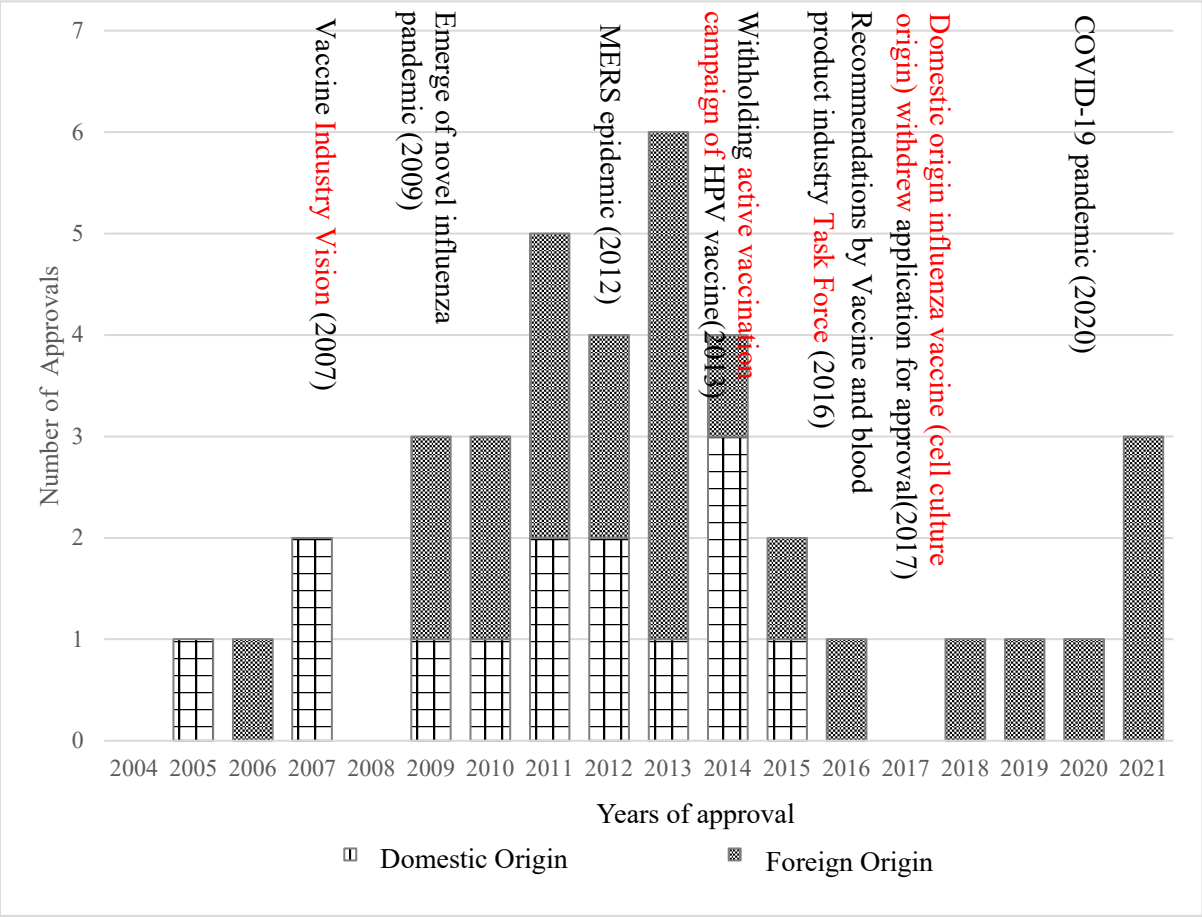

Figure 2. Number of participants in full analysis set of the conducted clinical trials

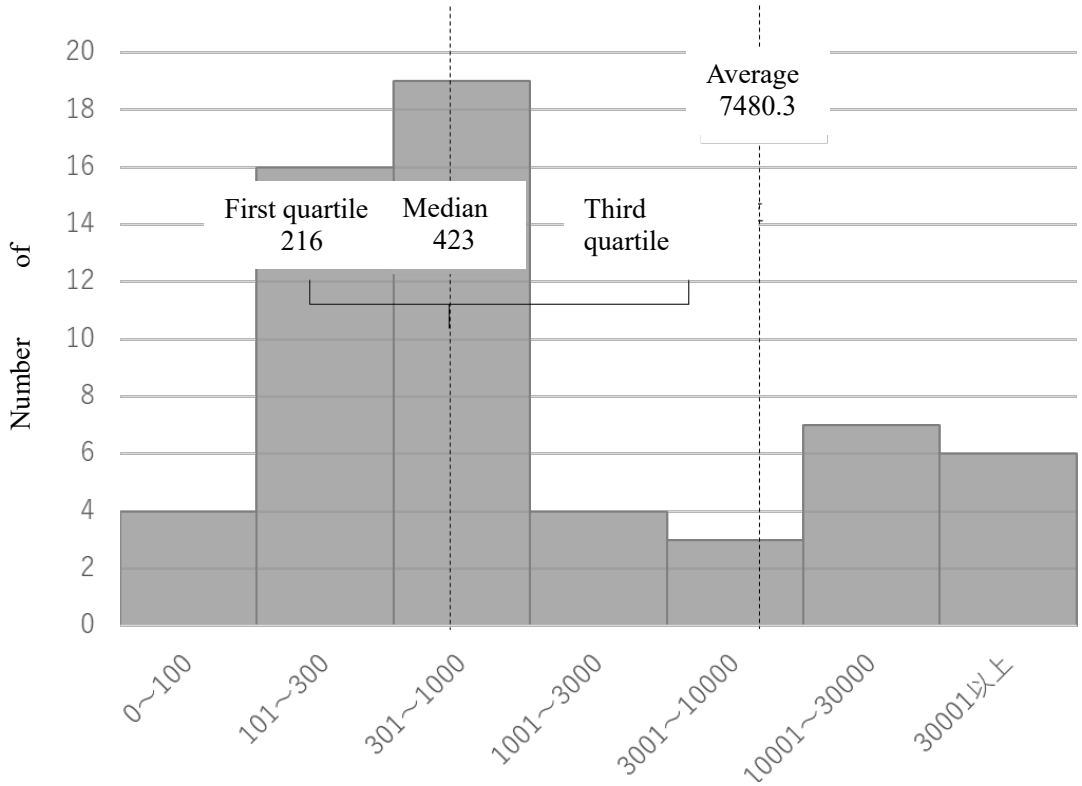

Figure 3. Number of participants in full analysis set of the conducted clinical trials (cross-analysis by domestic and foreign entities)

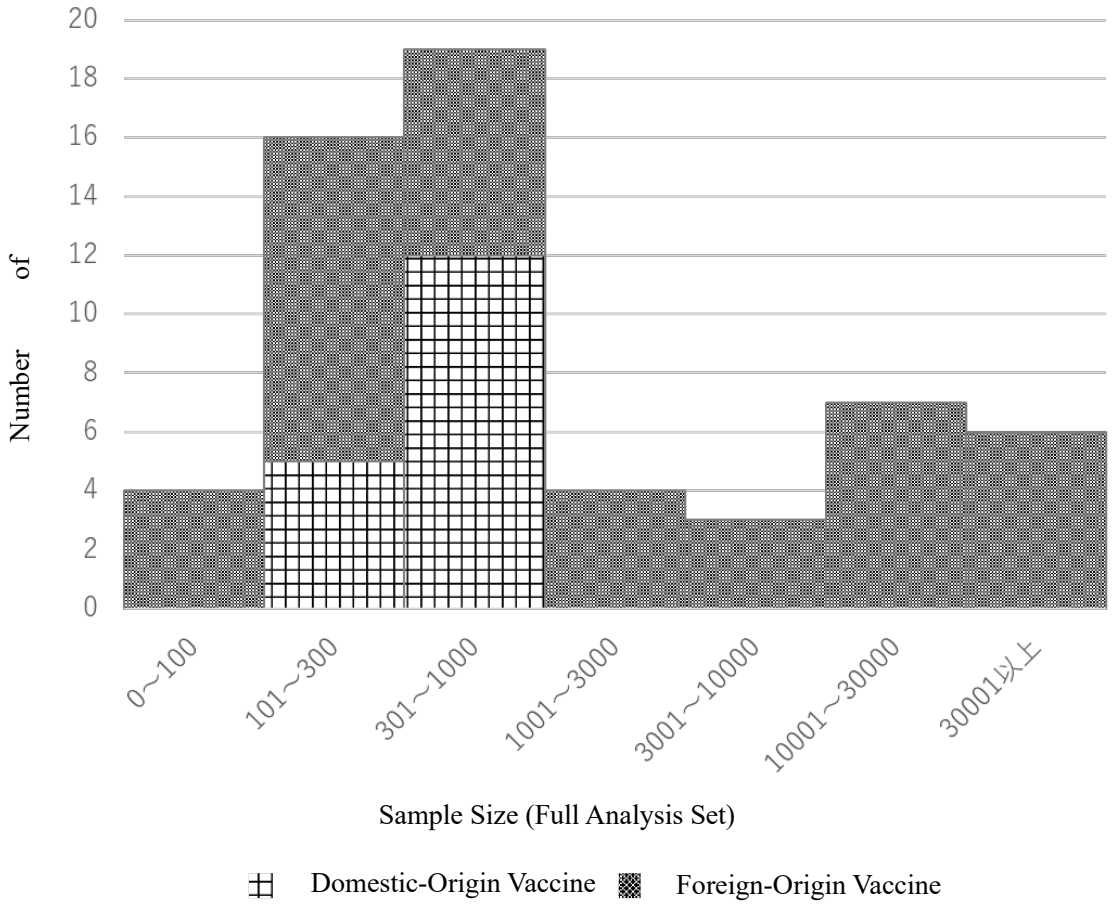

Table 2. Full analysis set of the clinical trials conducted (cross-analysis by domestic or foreign entities)

Number of participants in the full analysis set	Domestic origin (number of studies)	Percentage	Foreign origin (number of studies)	Percentage	Total
0～100	0	0.0%	4	9.5%	4
101～300	5	29.4%	11	26.2%	16
301～1000	12	70.6%	7	16.7%	19
1001～3000	0	0.0%	4	9.5%	4
3001～10000	0	0.0%	3	7.1%	3
10001～30000	0	0.0%	7	16.7%	7

30001 or more	0	0.0%	6	14.3%	6
Total	17	100.0%	42	100.0%	59

Figure 4. Relationship between the number of participants included in the analysis set and the primary evaluation of efficacy in the study.

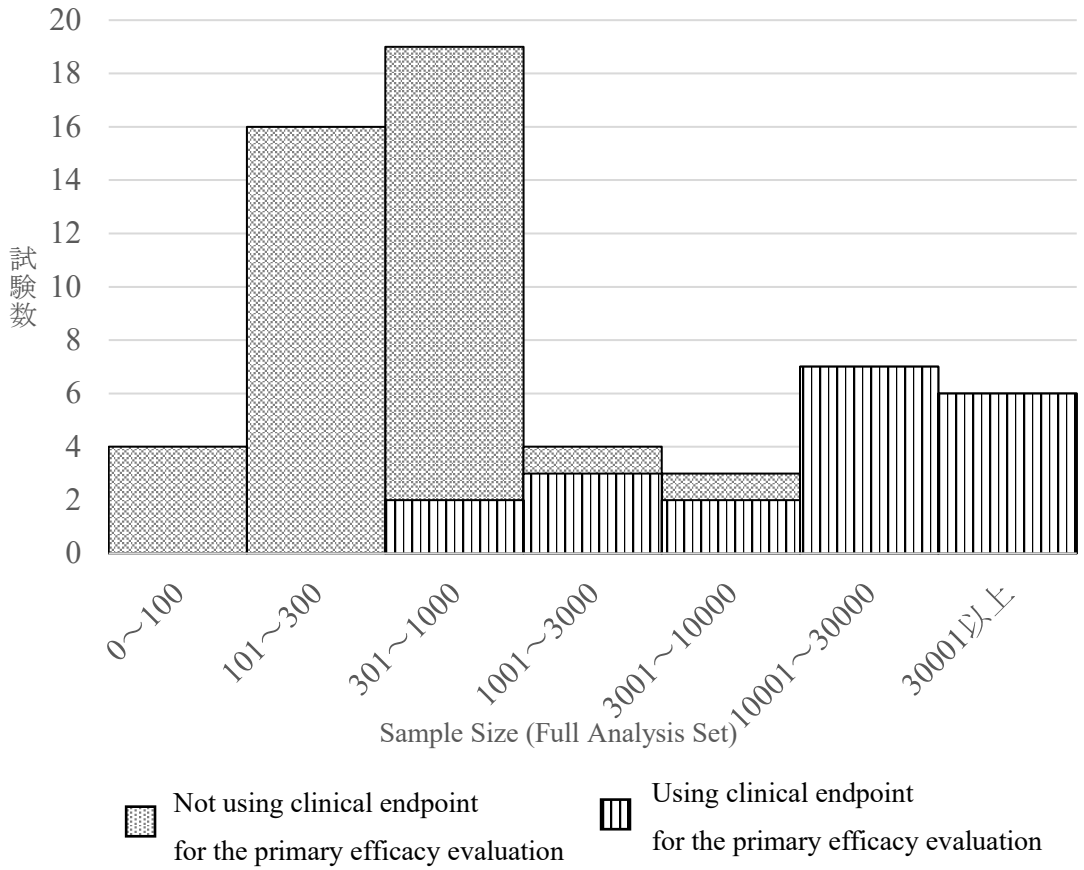

Table 3. Relationship between the number of participants included in the analysis of the clinical trial and the primary evaluation of efficacy (cross-tabulation by domestic and foreign entities)

Number of participants in the full analysis set	Clinical studies not using clinical endpoints for the primary efficacy evaluation		Clinical studies not using clinical endpoints to assess primary efficacy evaluation	
	Domestic origin	Foreign origin	Domestic origin	Foreign origin
0～100	0	4	0	0
101～300	5	11	0	0
301～1000	12	7	0	2
1001～3000	0	4	0	3
3001～10000	0	3	0	2
10001～30000	0	7	0	7

30001 or more	0	6	0	6
Total	17	42	0	20

Table 4. Classification based on products in which region the clinical trial was conducted for efficacy evaluation in the review report.

(1) Classification based on the domestic and foreign origins of the development of the active ingredients of vaccines

	Domestic origin vaccine	Foreign origin vaccine
Clinical trials conducted only in Japan	17 (100.0%)	16 (38.1%)
Multi-regional clinical trials, including Japan	0 (0.0%)	3 (7.1%)
Clinical trials conducted only in foreign countries	0 (0.0%)	23 (54.8%)

(2) Classification based on the domestic and foreign origins of marketing authorization holder

	Domestic marketing authorization holders	Foreign-affiliated manufacturers and distributors
Clinical trials conducted only in Japan	20 (76.9%)	13 (31.0%)
Multi-regional clinical trials, including Japan	2 (7.7%)	1 (2.4%)
Clinical trials conducted only in foreign countries	4 (15.4%)	19 (45.2%)

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