Table 2. Baseline Attributes of Participants in Phase III Study

	Group M (Formulation M + OPV placebo)		Control Group (DTaP + OPV)	
	n (%)	95% CI (%)	n (%)	95% CI (%)
Participant, no.	221		121	
Sex				
Male	100 (45.2)	38.6–52.1	55 (45.5)	36.4–54.8
Female	121 (54.8)	47.9–61.4	66 (54.5)	45.2–63.6
Age (months)				
Median (min-max)	4 (3–11)	.5–4.6	4 (3–9)	.9–8.2
Preimmunization seropositive rate				
Pertussis				
PT	3 (1.4)	.3–3.9	2 (1.7)	.2–5.8
FHA	13 (5.9)	3.2–9.8	4 (3.3)	.9–8.2
Diphtheria	16 (7.2)	4.2–11.5	6 (5.0)	1.8–10.5
Tetanus	137 (62.0)	55.2–68.4	77 (63.6)	54.4–72.2
Poliovirus				
Sabin strain type 1	104 (47.1)	40.3–53.9	54 (45.0)	35.9–54.3
Sabin strain type 2	78 (35.3)	29.0–42.0	44 (36.7)	28.1–46.0
Sabin strain type 3	20 (9.0)	5.6–13.6	11 (9.2)	4.7–15.8

Group M received Formulation M and OPV placebo, Control group received DTaP and OPV.

Abbreviations: CI, confidence interval; DTaP, diphtheria-tetanus-acellular pertussis; FHA, filamentous hemagglutinin; OPV, oral polio vaccine; PT, pertussis toxoid.

injection-site erythema, but most participants were <Grade 3 (long diameter <5 cm). The most common systemic adverse reaction was pyrexia, but most participants were <Grade 3 (<39.0°C) in both groups. There were no statistically significant differences in the incidence of Grade 3 or more severe pyrexia between the 2 groups. Serious adverse reactions occurred in 2 participants. One participant in Group M was hospitalized due to convulsions that occurred 20 days after the first immunization with Formulation M. The patient recovered well 4 days after hospitalization. The doctor who took care of this patient commented that a relationship between this case and Formulation M was probably very low, however, it could not be completely denied. The other participant, in the Control group, was hospitalized due to pneumonia that occurred 22 days after the third immunization with DTaP. The patient recovered well 4 days after hospitalization. The doctor commented that a relationship could not be completely denied. Neither participant was withdrawn from the study due to the adverse reaction. Based on these results, it is considered that all adverse reactions were clinically acceptable.

DISCUSSION

The Phase II and Phase III clinical studies revealed that the DTaP-sIPV (Formulation M) induced a 100% seropositive rate not only for the 3 types of Sabin strains, but also for the virulent poliovirus strains (type 1: Mahoney strain, type 2: MEF-1 strain, type 3: Saukett strain) after the booster immunization. In the manufacturing of DTaP-sIPV, the addition of sIPV did not affect the immunogenicity of any DTaP component. Formulation M was well tolerated. Based on the immunogenicity and safety data obtained in these clinical studies, this DTaP-sIPV was approved and licensed for use in Japan in July 2012 prior to its worldwide approval.

DTaP-sIPV has been developed with 3 objectives. The first objective is to prevent VAPP while maintaining a high immunity against polio. Theoretically, VAPP will not occur if the OPV is replaced with an sIPV. In addition, the high immunization rate of sIPV is expected to be maintained with DTaP-sIPV by combining an sIPV with DTaP.

The second objective is to prevent paralytic poliomyelitis caused by VDPVs. The spread of VDPVs has been suppressed by enhancing the routine immunization with an OPV [3]. In this study, the titers of neutralizing antibodies against polioviruses induced by the DTaP-sIPV were higher than those induced by OPV. Simply comparing the neutralizing antibody titers may not be sufficient to evaluate the comparative strength of sIPV and OPV against poliovirus, because sIPV and OPV may have different mechanisms for protection against polio. However, it has been shown that neutralizing antibodies play a major role in the protection, considering the efficacy of passive immunization of gamma globulin and active immunization of cIPV to control wild-type polioviruses [22–25]. Therefore, the DTaP-sIPV may also be effective against VDPVs. In fact, transgenic mice immunized with an sIPV were protected against VDPV [26].

The third objective is to prevent paralytic poliomyelitis caused by wild-type viruses. While the eradication of polio caused by wild-type viruses is close to completion, the possibility of polio import cannot be ruled out, given a recent outbreak in China [27]. Therefore, it is very important to understand whether immunity induced by sIPV can prevent polio caused by wild-type polioviruses. The efficacy of DTaP-sIPV should have been evaluated in an efficacy study, but it was impossible to conduct such a study in Japan where polio has already been eradicated. Therefore, in this study we used the neutralizing antibody titer as a surrogate marker.

In the Phase II clinical study, the seropositive rate was 100% for the virulent poliovirus types 1, 2, and 3 after the booster immunization with Formulation M. The neutralizing antibody titer against virulent poliovirus strains was similar to that against corresponding Sabin types 2 and 3, but the titer against the virulent poliovirus type 1 tended to be lower than that

Table 3. Seropositive Rates and Geometric Mean Antibody Titers After Primary Immunization in Phase III Study

	Group M (Formulation M + OPV placebo) (n = 221)[a]		Control Group (DTaP + OPV) (n = 120)[a]		
Antigen	Seropositive Rate (%) (95% CI)	GMT (95% CI)	Seropositive Rate (%) (95% CI)	GMT (95% CI)	*P* value
Poliovirus					
Sabin strain type 1	100.0 (98.3–100.0)	11.02[b] (10.78–11.26)	27.5 (19.7–36.4)	2.41[b] (2.02–2.79)	<.001[c]
Sabin strain type 2	100.0 (98.3–100.0)	10.48[b] (10.32–10.64)	15.0 (9.1–22.7)	1.86[b] (1.57–2.15)	<.001[c]
Sabin strain type 3	100.0 (98.3–100.0)	10.79[b] (10.59–10.99)	7.5 (3.5–13.8)	1.38[b] (1.20–1.56)	<.001[c]
Pertussis					
PT (EU/mL)	98.6 (96.0–99.7)	39.0 (35.5–42.9)	99.2 (95.4–100.0)	39.2 (34.6–44.6)	<.001[d]
FHA (EU/mL)	99.1 (96.7–99.9)	62.0 (56.7–67.7)	100 (96.9–100.0)	77.5 (68.1–88.4)	<.001[d]
Diphtheria (IU/mL)	100.0 (98.3–100.0)	1.72 (1.57–1.89)	100.0 (96.9–100.0)	.982 (.858–1.123)	<.001[d]
Tetanus (IU/mL)	100.0 (98.3–100.0)	1.32 (1.18–1.47)	100.0 (96.9–100.0)	1.27 (1.08–1.48)	<.001[c]

Group M received Formulation M and OPV placebo, Control group received DTaP and OPV. Primary immunization consisted of 3 immunizations. Seropositive is $\geq 1{:}8(2^3)$.

Abbreviations: CI, confidence interval; DTaP, diphtheria-tetanus-acellular pertussis; EU, enzyme-linked immunosorbent assay units; FHA, filamentous hemagglutinin; GMT, geometric mean titer; IU, international units; OPV, oral polio vaccine; PT, pertussis toxoid.

[a] Immunogenicity population for Sabin polioviruses: 221 participants in Group M, 120 participants in Control group. Immunogenicity population for DTaP components: 217 participants in Group M, 119 participants in Control group.

[b] ($\log_2$).

[c] Superiority of Group M for Sabin polioviruses: 1-sample binomial test (to verify that null hypothesis [seropositive rate ≤90%] could be rejected).

[d] Noninferiority of Group M to the Control group for DTaP components: Farrington–Manning test (to verify that Group M was not inferior to the Control group by more than 10%) in seropositive rate.

Table 4. Seropositive Rates and Geometric Mean Antibody Titers After Booster Immunization in Phase III Study

	Group M (Formulation M + OPV placebo) (n = 218)[a]		Control Group (DTaP + OPV) (n = 119)[a]		
Antigen	Seropositive Rate (%) (95% CI)	GMT (95% CI)	Seropositive Rate (%) (95% CI)	GMT (95% CI)	*P* value
Poliovirus					
Sabin strain type1	100.0 (98.3–100.0)	12.13[b] (11.93–12.33)	97.5 (92.8–99.5)	11.55[b] (11.10–12.01)	<.001[c]
Sabin strain type2	100.0 (98.3–100.0)	12.61[b] (12.46–12.77)	99.2 (95.4–100.0)	9.62[b] (9.29–9.95)	<.001[c]
Sabin strain type3	100.0 (98.3–100.0)	12.22[b] (12.03–12.42)	83.2 (75.2–89.4)	7.12[b] (6.55–7.69)	<.001[c]
Pertussis					
PT (EU/mL)	100.0 (98.3–100.0)	196 (175–220)	100 (96.9–100.0)	187 (163–214)	<.001[d]
FHA (EU/mL)	100.0 (98.3–100.0)	255 (232–279)	100 (96.9–100.0)	305 (273–342)	<.001[d]
Diphtheria (IU/mL)	100.0 (98.3–100.0)	18.0 (16.3–19.9)	100 (96.9–100.0)	11.9 (10.5–13.6)	<.001[d]
Tetanus (IU/mL)	100.0 (98.3–100.0)	5.4 (4.76–6.12)	100 (96.9–100.0)	4.36 (3.68–5.17)	<.001[d]

Group M received Formulation M and OPV placebo, Control group received DTaP and OPV. Booster immunization was the fourth immunization. Seropositive is $\geq 1{:}8(2^3)$.

Abbreviations: CI, confidence interval; DTaP, diphtheria-tetanus-acellular pertussis; EU, enzyme-linked immunosorbent assay units; FHA, filamentous hemagglutinin; GMT, geometric mean titer; IU, international units; OPV, oral polio vaccine; PT, pertussis toxoid.

[a] Immunogenicity population for Sabin polioviruses: 218 participants in Group M, 119 participants in Control group. Immunogenicity population for DTaP components: 214 participants in Group M, 118 participants in Control group, whose blood samples were collected.

[b] ($\log_2$).

[c] Superiority of Group M for Sabin polioviruses: 1-sample binomial test (to verify that null hypothesis [seropositive rate ≤90%] could be rejected).

[d] Noninferiority of Group M for DTaP components: Farrington–Manning test (to verify that Group M was not inferior to Control group by more than 10%) in seropositive rate.

Table 5. Adverse Reactions in Phase III Study

	Group M (Formulation M + OPV placebo)		Control Group (DTaP + OPV)	
Adverse reaction	n (%)	95% CI (%)	n (%)	95% CI (%)
Participants, no.	221		121	
Injection-site reaction				
Injection-site erythema	151 (68.3%)	61.8–74.4	79 (65.3%)	56.1–73.7
≥Grade 3 (long diameter 5 cm)	11 (5.0%)	2.5–8.7	8 (6.6%)	2.9–12.6
Injection-site induration	115 (52.0%)	45.2–58.8	67 (55.4%)	46.1–64.4
Injection-site swelling	69 (31.2%)	25.2–37.8	41 (33.9%)	25.5–43
≥Grade 3 (long diameter 5 cm)	5 (2.3%)	.7–5.2	6 (5.0%)	1.8–10.5
Systemic reaction				
Pyrexia[a]	123 (55.7%)	48.8–62.3	56 (46.3%)	37.2–55.6
≥Grade 3 (39.0°C)	22 (10.0%)	6.3–14.7	13 (10.7%)	5.8–17.7
Diarrhea	91 (41.2%)	34.6–48	40 (33.1%)	24.8–42.2
≥Grade 3 (9 times/day)	4 (1.8%)	.5–4.6	1 (0.8%)	0–4.5
Mood altered	69 (31.2%)	25.2–37.8	26 (21.5%)	14.5–29.9
Rhinorrhea	41 (18.6%)	13.7–24.3	23 (19.0%)	12.4–27.1
Cough	35 (15.8%)	11.3–21.3	15 (12.4%)	7.1–19.6
Rash	28 (12.7%)	8.6–17.8	11 (9.1%)	4.6–15.7
Vomiting	26 (11.8%)	7.8–16.8	16 (13.2%)	7.8–20.6
≥Grade 3 (6 times/day)	2 (0.9%)	.1–3.2	1 (0.8%)	0–4.5
Decreased appetite	26 (11.8%)	7.8–16.8	10 (8.3%)	4–14.7
Pharyngeal erythema	25 (11.3%)	7.5–16.2	8 (6.6%)	2.9–12.6
Productive cough	12 (5.4%)	2.8–9.3	5 (4.1%)	1.4–9.4

Group M received Formulation M and OPV placebo, Control group received DTaP and OPV. Adverse reactions with an incidence of ≥5% in any group are listed.

Abbreviations: CI, confidence interval; DTaP, diphtheria-tetanus-acellular pertussis; OPV, oral polio vaccine.

[a] Defined as axillary temperature of ≥37.5°C.

against corresponding Sabin type 1, although being much higher than the protective level. Subsequently, the neutralizing antibody concentrations (IU/mL) were calculated using the international standard serum provided by the National Institute for Biological Standards and Control for comparison with the previously reported results of clinical studies of cIPV, as shown in Table 6 [28, 29]. The concentration of neutralizing antibody against virulent type 1 induced by Formulation M after the

Table 6. Comparison of Concentration (IU/mL) of Neutralizing Antibodies against Virulent Poliovirus Strains Induced by DTaP-sIPV and cIPVs

	Neutralizing Antibody Concentration (IU/mL, geometric mean)[a] (95% CI)					
	After Primary Immunization[b]			After Booster Immunization		
Vaccine	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3
DTaP-sIPV (Formulation M)	1.5 (1.1–1.9)	10 (7.2–14)	4.4 (3.1–6.2)	9.1 (5.7–14)	240 (150–360)	57 (40–82)
cIPV (IPV-A)[c]	2.1	3.6	5.0	13	25	16
cIPV (IPV-B)[c]	1.3	6.8	3.3	8.0	28	18

Abbreviations: CI, confidence interval; cIPV, conventional IPV produced using virulent polioviruses; DTaP, diphtheria-tetanus-acellular pertussis; IPV, inactivated polio vaccine; IU, international units; OPV, oral polio vaccine; sIPV, IPV using attenuated Sabin strains.

[a] The neutralizing antibody titers (log_2) were converted into the neutralizing antibody concentrations (IU/mL) using international standard serum provided by the National Institute for Biological Standards and Control.

[b] DTaP-sIPV and cIPV were administered in 3 doses and 2 doses, respectively, for primary immunization.

[c] Data were cited from reference No. 28.

primary and booster immunizations was comparable to that after the primary and booster immunizations with a cIPV, indicating that Formulation M is expected to prevent polio caused by wild-type polioviruses as effectively as the cIPV with an established efficacy. In a similar analysis for virulent types 2 and 3, the antibody concentration after the primary and booster immunizations with Formulation M was equal to or higher than that with cIPV, strongly suggesting that DTaP-sIPV is also effective for wild-type polioviruses.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. WHO. Wild Poliovirus 2007–2012. http://www.polioeradication.org/Portals/0/Document/Data&Monitoring/Wild_poliovirus_list_2007_2012_06June.pdf. Accessed 7 December 2012.
2. Hao L, Toyokawa S, Kobayashi Y. Poisson-model analysis of the risk of vaccine-associated paralytic poliomyelitis in Japan between 1971 and 2000. Jpn J Infect Dis **2008**; 61:100–3.
3. Sutter RW, Kew OM, Cochi SL. Poliovirus vaccine-live. In: Plotkin SA, Orenstein WA, Offit P, eds. Vaccines. 5th ed. Saunders Elsevier, **2008**: 631–85.
4. WHO global action plan to minimize poliovirus facility-associated risk after eradication of wild polioviruses and cessation of routine OPV use. http://www.polioeradication.org/Portals/0/Document/Resources/PostEradication/GAP3_2009.pdf. Accessed 7 December 2012.
5. Kreeftenberg H, van der Velden T, Kersten G, van der Heuvel N, de Bruijn M. Technology transfer of Sabin-IPV to new developing country markets. Biologicals **2006**; 34:155–8.
6. Bakker WA, Thomassen YE, van't Oever AG, et al. Inactivated polio vaccine development for technology transfer using attenuated Sabin poliovirus strains to shift from Salk-IPV to Sabin-IPV. Vaccine **2011**; 29:7188–96.
7. Murph JR, Grose C, McAndrew P, et al. Sabin inactivated trivalent poliovirus vaccine: first clinical trial and seroimmunity survey. Pediatr Infect Dis J **1988**; 7:760–5.
8. Doi Y, Abe S, Yamamoto H, et al. Progress with inactivated poliovirus vaccines derived from the Sabin strains. Dev Biol (Basel) **2001**; 105: 163–9.
9. Liao G, Li R, Li C, et al. Safety and immunogenicity of inactivated poliovirus vaccine made from Sabin strains: a phase II, randomized, positive-controlled trial. J Infect Dis **2012**; 205:237–43.
10. Simizu B, Abe S, Yamamoto H, et al. Development of inactivated poliovirus vaccine derived from Sabin strains. Biologicals **2006**; 34:151–4.
11. Kersten G, Hazendonk T, Beuvery C. Antigenic and immunogenic properties of inactivated polio vaccine made from Sabin strains. Vaccine **1999**; 17:2059–66.
12. Ginnaga A, Morokuma K, Aihara K, et al. Characterization and clinical study on the acellular pertussis vaccine produced by a combination of column purified pertussis toxin and filamentous hemagglutinin. Tokai J Exp Clin Med **1988**; 13(Suppl):59–69.
13. Kimura M, Kuno-Sakai H, Kamiya H, et al. Immunogenicity and reactogenicity of the component acellular pertussis vaccine produced by a combination of column purified pertussis toxin and filamentous haemagglutinin. Acta Paediatr Jpn **1995**; 37:562–74.
14. Huang LM, Lee CY, Lin TY, Chen JM, Lee PI, Hsu CY. Responses to primary and a booster dose of acellular, component, and whole-cell pertussis vaccines initiated at 2 months of age. Vaccine **1996**; 14: 916–22.
15. Kuno-Sakai H, Kimura M. Safety and efficacy of acellular pertussis vaccine in Japan, evaluated by 23 years of its use for routine immunization. Pediatr Int **2004**; 46:650–5.
16. Okada K, Ohashi Y, Matsuo F, Uno S, Soh M, Nishima S. Effectiveness of an acellular pertussis vaccine in Japanese children during a non-epidemic period: a matched case-control study. Epidemiol Infect **2009**; 137:124–30.
17. Manual for the virological investigation of poliomyelitis. WHO/EPI/CDS/POLIO/90.1. http://whqlibdoc.who.int/hq/1990/WHO_EPI_CDS_POLIO_90.1.pdf. Accessed 7 December 2012.
18. Plotkin SA, Vidor E. Poliovirus vaccine-inactivated. In: Plotkin SA, Orenstein WA, Offit P, eds. Vaccines. 5th ed. Saunders Elsevier, **2008**:605–29.
19. Kato T. DPT. J Pediatr Practice **1990**; 53:2275–81.
20. Vitek CR, Wharton M. Diphtheria toxoid. In: Plotkin SA, Orenstein WAOffit P, eds. Vaccines. 5th ed. Saunders Elsevier, **2008**; 139–56.
21. Wassilak SGF, Roper MH, Kretsinger K, Orenstein WA. Tetanus toxoid. In: Plotkin SA, Orenstein WA, Offit P, eds. Vaccines. 5th ed. Saunders Elsevier, **2008**;805–39.
22. Francis TJ, Korns RF. Evaluation of 1954 field trial of poliomyelitis vaccine: synopsis of summary report. Am J Med Sci **1955**; 229:603–12.
23. Melnick JL, Benyesh-Melnick M, Pena R, Yow M. Effectiveness of Salk vaccine. Analysis of virologically confirmed cases of paralytic and nonparalytic poliomyelitis. J Am Med Assoc **1961**; 175:1159–62.
24. Robertson SE, Traverso HP, Drucker JA, et al. Clinical efficacy of a new, enhanced-potency, inactivated poliovirus vaccine. Lancet **1988**; 331: 897–9.
25. Hammon WM, Coriell LL, Wehrle PF, Stokes J Jr. Evaluation of Red Cross gamma globulin as a prophylactic agent for poliomyelitis. 4. Final report of results based on clinical diagnoses. J Am Med Assoc **1953**; 151:1272–85.
26. Dragunsky EM, Ivanov AP, Wells VR, et al. Evaluation of immunogenicity and protective properties of inactivated poliovirus vaccines: a new surrogate method for predicting vaccine efficacy. J Infect Dis **2004**; 190:1404–12.
27. WHO. Confirmed international spread of wild poliovirus from Pakistan. http://www.who.int/csr/don/2011_09_20/en/index.html. Accessed 7 December 2012.
28. National Institute for Biological Standards and Control. WHO International Standard Anti-Measles Serum, Human and Anti-Poliovirus serum Types 1,2 and 3. (66/202). http://www.nibsc.ac.uk/documents/ifu/66-202.pdf. Accessed 7 December 2012.
29. McBean AM, Thoms ML, Albrecht P, Cuthie JC, Bernier R. Serologic response to oral polio vaccine and enhanced-potency inactivated polio vaccine. Am J Epidemiol. **1988**; 128:615–28.

特集　変貌を遂げつつあるわが国の予防接種体制

日本脳炎ワクチン

宮崎千明

キーワード：日本脳炎，乾燥細胞培養日本脳炎ワクチン，定期接種，急性散在性脳脊髄炎

はじめに

日本脳炎はコガタアカイエカによって媒介され，日本脳炎の発症頻度は感染者100～1,000人に1人とされている．わが国では1960年代半ばまで年間数千人の日本脳炎患者が発生していたが，1990年代以降，年間10人未満（平均6人）で推移している[1]．関東以西，特に九州，中国，四国ではウイルスの増幅動物とされるブタの感染率が高く，その地域の患者発生が多くみられる．ウイルスは東南アジアや東アジアから持ち込まれる株も含めて，依然としてわが国に広く存在しており，日本脳炎の脅威は継続している．

I 日本脳炎抗体保有状況

2005年5月にマウス脳由来ワクチンの積極的勧奨が突如差し控えられ，2006年度の1期初回のワクチン実施率は5%以下に低下した．乾燥細胞培養日本脳炎ワクチン（以下，日本脳炎ワクチンと略）の上市とそれに伴う接種勧奨再開によって，幼児の抗体保有率は再上昇したが，2005～2012年の8シーズンに熊本，高知，山口，沖縄，福岡で計6例（1～10歳）が報告された．国立感染症研究所感染症疫学センターの感染症流行予測調査（2012年度）では，幼児期の抗体保有率は接種勧奨差し控え以前に戻りつつある[2]．また中高年の陽性率も低いが，抗体陰性者の多くは小児期のワクチン免疫が経時的に低下したのではないかと考えられ，小児から成人のおよそ20%がわが国では日本脳炎ウイルスに対する免疫を全くもたない感受性者であると推測される．

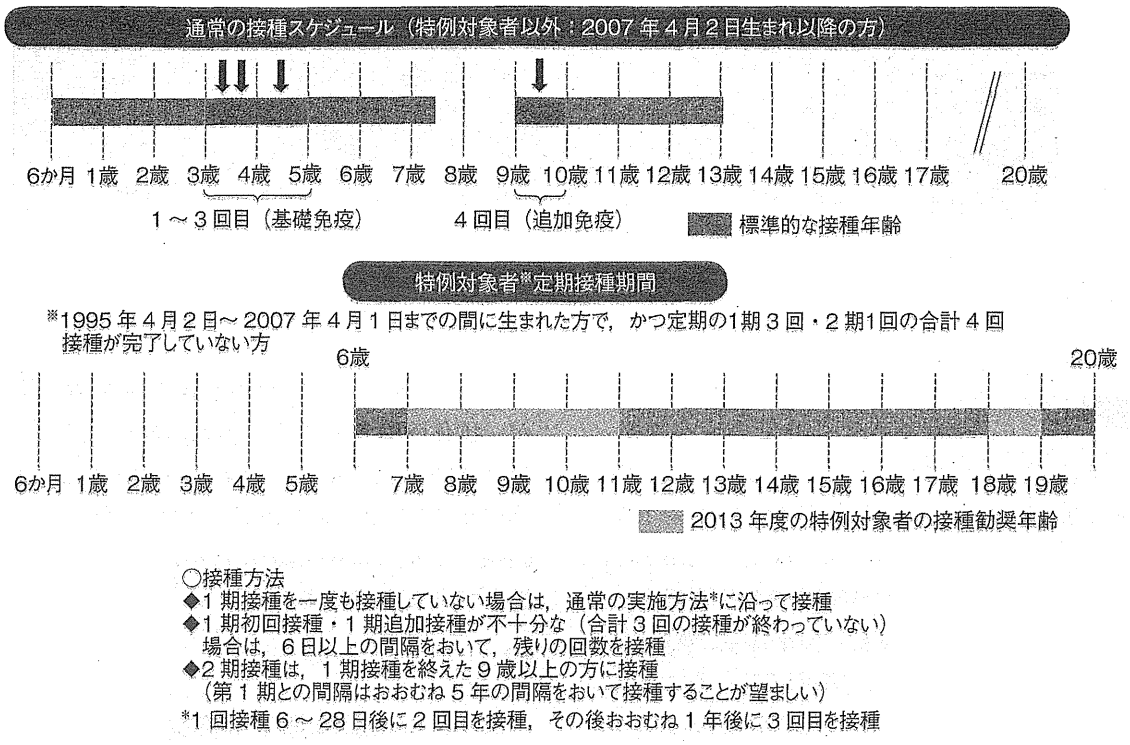
II 日本脳炎ワクチン

ADEM（急性散在性脳脊髄炎）の理論的リスクの軽減，未知の感染性因子の混入リスクの低減，安定的ワクチン供給，動物愛護などの観点から，日本脳炎ワクチンが開発された．マウス脳由来ワクチンと同様に北京株ウイルスをVero細胞で増殖させ，不活化した凍結乾燥製剤で保存剤は含まない．マウス脳由来ワクチンに比べて少ない抗原量で良好な抗体価が得られている[3]．1期初回免疫（2回接種）で数百倍，追加接種後に数千倍の中和抗体価が得られ，抗体価が再上昇する．

III 積極的勧奨の再開

2009年6月，日本脳炎ワクチン（ジェービックV®）の発売と同時に1期の定期接種としての使用が始まり，現在に至るまで数度にわたる段階的なワクチン接種に関する積極的勧奨の拡大や定期接種年齢の拡大が図られた．2011年4月にエンセバック®が発売され，同年5月に

Japanese encephalitis vaccine
Chiaki Miyazaki : Fukuoka-West Rehabilitation Center for Children
福岡市立西部療育センター長



○接種方法
◆1期接種を一度も接種していない場合は，通常の実施方法*に沿って接種
◆1期初回接種・1期追加接種が不十分な（合計3回の接種が終わっていない）場合は，6日以上の間隔をおいて，残りの回数を接種
◆2期接種は，1期接種を終えた9歳以上の方に接種
（第1期との間隔はおおむね5年の間隔をおいて接種することが望ましい）
*1回接種6～28日後に2回目を接種，その後おおむね1年後に3回目を接種

図1　日本脳炎ワクチンに関する定期接種対象者（2013年4月1日施行）
（厚生労働省健康局長，医薬食品局長：「日本脳炎の定期の予防接種について」の一部改正について．健発0228第2号，薬食発0228第1号，平成24年2月28日より引用，作成）

積極的勧奨の差し控えの間に接種機会を逃した特例対象者（1995年6月1日～2007年4月1日生まれの者．現在は1995年4月2日～2007年4月1日生まれの者に拡大された）に対しては，20歳未満まで定期接種とする政令改正を行い，免疫ギャップの解消を図った[4]．

Ⅳ 接種方法

日本脳炎ワクチンは，通常，6～90か月未満に，標準的には3歳で1期初回として6～28日までの間隔をおいて2回接種し，おおむね1年後に1回追加接種する．9～13歳未満で，1期からおおむね5年以上あけて2期接種として1回接種する（図1）．1期の追加接種はおおむね1年後となっているが，間隔を厳密に考える必要はなく，接種間隔がおおむね1年を超えても，また1年に満たなくても有効である．

日本脳炎ワクチンの要点は接種回数を重視して，最低3回の接種を行って基礎免疫をつけることである．そして一定間隔をあけて4回目の接種を行う．4回目の接種は長期免疫効果を考えると，規定の範囲内で間隔を広くあけたほうがより効果的である．間隔が広くあいたからといって，最初から接種をやり直す必要はなく，規定の回数を接種する[3,4]．

Ⅴ 日本脳炎ワクチンの副反応に関する情報

ワクチンの主な副反応は発熱，注射部位の紅斑・腫脹，発疹などで，重篤な副反応の報告は少ない．しかし，日本脳炎ワクチンといえども，因果関係のない紛れ込みも含めれば，接種後のある一定期間にADEMは起こりうると思われる．

2012年に，日本脳炎ワクチンを接種した後に2例の死亡例や，その他のADEM症例などが報告されたが，因果関係や頻度の検討からワクチン接種を中止せず，副反応の報告と解析を進めることになった[5]．2013年4月の予防接種法改正によって，定期接種ワクチンの副反応の報告が義務化され，それに対応して報告基準も見直された．日本脳炎ワクチンの1回目の接種ではマウス脳ワクチンに比べて発熱率がやや高い傾向にあるが，2回目以降は差がなく，抗体上昇は良い．

おわりに

現在，わが国における日本脳炎の発生数は年間10名以下であるが，海外では東南アジアを中心に年間数万人の患者発生がみられる[6]．ワクチンを導入した国では患者が減少しているが，そうでない国ではむしろ増加している．中国では生ワクチンを使用しているが，安全性の確認が十分でない．海外にはアジュバントを含有した日本脳炎ワクチンもあるが，わが国の日本脳炎ワクチンはより高い抗体を獲得できる．今後も疾患の発生とワクチンの副反応を監視しながら疾患ゼロを目指したい．

文　献

1) 国立感染症研究所ウイルス第一部：日本脳炎疾患情報. http://www.nih.go.jp/niid/ja/diseases/na/je.html
2) 国立感染症研究所感染症疫学センター：2012年度感染症流行予測調査 日本脳炎. http://www.nih.go.jp/niid/ja/y-graphs/3505-je-yosoku-year2012.html
3) 宮崎千明：予防接種各論 日本脳炎ワクチン―乾燥細胞培養ワクチンと接種勧奨の再開. 医のあゆみ 2013；244：79-85.
4) 厚生労働省：日本脳炎ワクチン接種に係るQ＆A. 平成25年3月改訂版. http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou21/dl/nouen_qa.pdf
5) 厚生労働省：第8回厚生科学審議会感染症分科会予防接種部会日本脳炎に関する小委員会及び平成24年度第6回薬事・食品衛生審議会医薬品等安全対策部会安全対策調査会資料. 平成24年12月13日. http://www.mhlw.go.jp/stf/shingi/2r9852000002r5cg.html
6) Erlanger TE, Weiss S, Keiser J, *et al*：Past, present, and future of Japanese encephalitis. *Emerg Infect Dis* 2009；15：1-7. http://wwwnc.cdc.gov/eid/article/15/1/08-0311_article.htm

予防接種 Q&A

日本脳炎―勧奨中止による未接種者への対応

176. 勧奨中止により接種できなかった人のための対策はどのようになっていますか

回答・解説　宮崎千明*

回答要旨

国による接種勧奨の差し控えにより接種機会を逸した者（特例対象者）は，20歳未満まで1期3回と2期接種の計4回を定期接種として接種できる。不活化ワクチンの原則に従い，接種間隔より接種回数を重視する。

解説

平成17（2005）年5月30日～平成22（2010）年3月31日にかけて，日本脳炎の標準的な接種年齢（第1期：3～4歳，第2期：9歳）に積極的な勧奨が行われていないと考えられる平成7（1995）年6月1日～平成19（2007）年4月1日までに生まれた児について，4～20歳になるまでの間（20歳未満），日本脳炎の定期予防接種を受けることができるようになった〔平成23（2011）年5月20日予防接種法施行令改正〕[1,2]。その後，同じ学年での不公平の解消のため，平成25（2013）年4月1日から，平成7年4月2日～5月31日生まれの者も特例対象者に加えられた（平成25年2月1日政令改正公布，4月1日施行）[3]。

図1に厚生労働省が提示した，特例対象者への接種スケジュールの目安を示したので参照いただきたい。不活化ワクチンである日本脳炎ワクチン接種の要点は，接種回数を重視して，最低3回の接種を行って基礎免疫をつけ，一定間隔をあけて4回目の接種を行う。長期の免疫持続を期待すれば，4回目の接種は規定の範囲内で間隔が広くあいた方がより効果的である。各接種間の間隔が広くあいたからといって最初から接種をやり直す必要はなく，規定の回数を接種する。6日以上と記載されている部分があるが，図内の注釈にもあるように，これは最短の接種間隔である。不活化ワクチンの常識として，短期間に連続する場合には4～8週程度間隔をあける方が免疫反応はよりよくなり，3回の接種が終わっていれば最低5年程度（あるいはそれ以上）は抗体が持続することがわかってきたので，定期接種できる年齢の上限に近い時期に接種してもよい。しかしその場合，間があきすぎて本人が追加接種を忘れてしまうリスクもあるので，それも勘案する。

また，平成19年4月2日～平成21（2009）年10月1日に生まれで，平成22年3月31日以前に，第1期の接種（計3回）を受ける機会を逃した児は，本来の定期接種年齢の期間内に不足分の回数を予防接種法に基づいて接種できる（予防接種実施規則平成22年8月）が，接種漏れ者に対する不規則接種についてはさまざまなパターンがあるので，これも国が例示しているので参照いただきたい（**図2**）[1]。

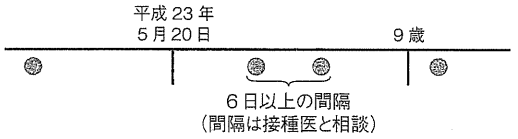
Key words：日本脳炎ワクチン，特例対象者，接種間隔

文献

1）厚生労働省：日本脳炎ワクチンに係るQ＆A（平成25年3月改訂版）　http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou21/dl/nouen_qa.pdf（2013年6月18日アクセス）
2）宮崎千明：日本脳炎ワクチン．医学のあゆみ**244**：79-85，2013
3）厚生労働省：予防接種法施行令の一部を改正する政令の施行等について　http://www.jata.or.jp/dl/pdf/law/2013/20130201.pdf

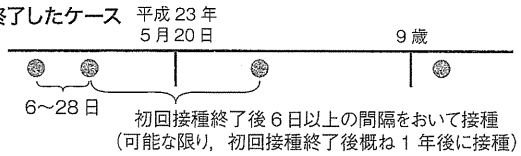
MIYAZAKI Chiaki
*福岡市立西部療育センター
〔〒819-0005　福岡市西区内浜1-5-54〕
TEL 092-883-7161

① 初回接種のうち 1 回のみ終了したケース



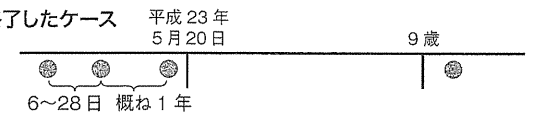
第 1 期終了後，6 日以上の間隔をおいて接種
（第 1 期との間隔は概ね 5 年の間隔をおいて接種することが望ましい）
（なお，1 回目と 2 回目の間隔が 5 年以上空いている場合は，3 回目と 4 回目の間隔は，概ね 1 年の間隔をおいて接種することが望ましい）

② 初回接種が終了したケース



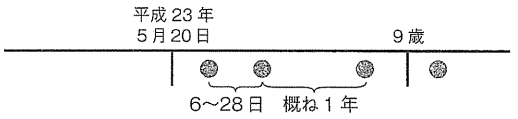
第 1 期終了後，6 日以上の間隔をおいて接種
（第 1 期との間隔は概ね 5 年の間隔をおいて接種することが望ましい）

③ 第 1 期が終了したケース



第 1 期終了後，6 日以上の間隔をおいて接種
（第 1 期との間隔は概ね 5 年〔以上〕の間隔をおいて接種することが望ましい）

④ 日本脳炎の予防接種を全く受けていないケース



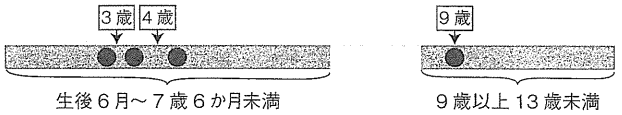
第 1 期終了後，6 日以上の間隔をおいて接種
（第 1 期との間隔は概ね 5 年〔以上〕の間隔をおいて接種することが望ましい）

2. 任意接種を含むケースについて

任意接種については，法令上は接種回数にカウントしないが，運用上はカウントしたうえで接種間隔を決定して差し支えない。
経過措置の趣旨は，接種する機会を与えることであるため，既に必要回数の接種が完了している者について接種する必要はない。

図 1　政令改正で日本脳炎ワクチンの定期接種対象になった年齢（H7.4.2*～H19.4.1 生まれ；対象期間：20 歳未満）への接種（*平成 25 年 4 月 1 日から施行）
〔厚生労働省：日本脳炎ワクチン接種に係る Q & A（平成 23 年 7 月改訂版）より引用改変〕

標準的な接種スケジュール（※平成 19 年 4 月 2 日生まれ以降の方はこのスケジュール）

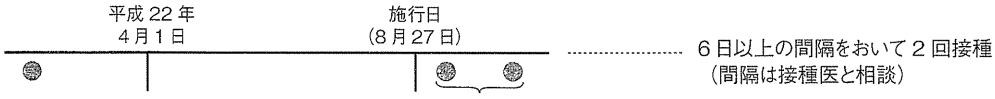


第 1 期：3 歳から 4 歳までに 6 日～ 28 日の間隔をおいて 2 回，その後概ね 1 年の間隔をおいて，4 歳から 5 歳までの間で 1 回接種。
第 2 期：9 歳から 10 歳までの間に 1 回接種。

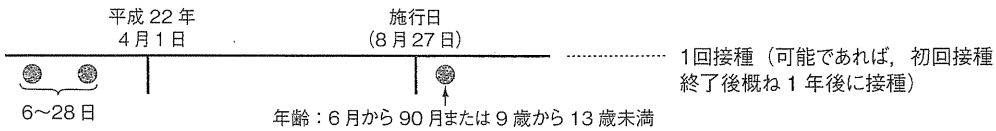
接種機会を逃した方に対する標準的な接種スケジュール（例）

（平成 19 年 4 月 2 日～ 21 年 10 月 1 日生まれ）（対象期間：6 月から 90 月，9 歳から 13 歳未満）

① 平成 22 年 3 月 31 日までに初回接種のうち 1 回のみ終了したケース



② 平成 22 年 3 月 31 日までに初回接種が終了したケース



③ 平成 22 年 3 月 31 日までに，全く接種していない対象者（9 歳から 13 歳未満）

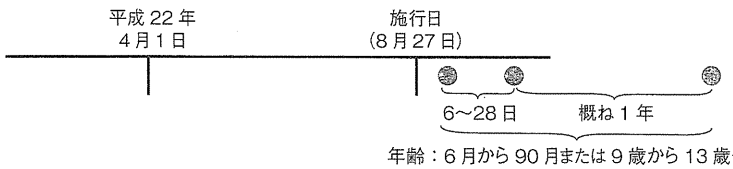


図 2　日本脳炎ワクチンの標準的なスケジュールと接種が遅れた者の接種
〔厚生労働省：日本脳炎ワクチン接種に係る Q & A（平成 23 年 7 月改訂版）より引用改変〕

特集

予防接種法改正
予防接種とワクチンの現状 13
○定期接種 A

Key words
日本脳炎
乾燥細胞培養日本脳炎ワクチン
急性散在性脳脊髄炎
定期接種

日本脳炎

宮崎 千明（みやざき ちあき）*

要旨

わが国の日本脳炎患者は年間10人未満であるが，日本脳炎ウイルスは西日本を中心になお広く蔓延している．乾燥細胞培養日本脳炎ワクチンがわが国で開発され，2009年6月から接種が始まった．2010年4月に標準的接種年齢（3歳）で積極的勧奨が再開されて以降，勧奨の拡大と定期接種対象者の拡大がはかられた．2012年秋に有害事象例の検討が行われたが，接種勧奨は継続された．2013年には2期接種の勧奨も再開され，日本脳炎ワクチンの免疫ギャップはさらに埋められていく．今後も副反応に注意しながら，広く接種を進めていきたい．

はじめに

国内で開発された乾燥細胞培養日本脳炎ワクチン（ジェービックV®：2009年，エンセバック®皮下注：2011年）を使い，順次接種勧奨が再開された．その結果，2005年5月以来の積極的勧奨の差し控えによって予防接種を受けていない小児に対しても接種が進み，小児における日本脳炎の免疫ギャップは埋まりつつある．同時に市販後の安全性と効果の検証も同時進行で行われており，2012年秋に報告された接種後の死亡例や急性散在性脳脊髄炎（acute disseminated encephalomyelitis：ADEM）症例の検討の結果，接種勧奨は継続されることになり，2013年4月から2期接種の勧奨も始まった．

本稿では，日本脳炎の現状とワクチンの有効性・安全性および積極的勧奨の拡大，接種の実際等について解説する．

* 福岡市立西部療育センター小児科
〒819-0005 福岡県福岡市西区内浜1-5-54

I 日本脳炎の発生動向

わが国では1960年代まで年間数千人の日本脳炎患者が発生していたが，マウス脳由来ワクチンの開発（1954年）とその勧奨接種により発症者は減少した．1967年から小児と成人へのワクチン接種特別対策が展開され，1976年の予防接種法改正で臨時接種に位置づけられ，1980年代には年間発症者が数十人程度になった．1989年にワクチンウイルス株が中山株から北京株（野外株に対してより広く免疫原性を誘導できる）に変更された．

1994年の予防接種法改正により1995年から定期接種となり，主に個別接種で実施されるようになった．1991年以降，わが国における日本脳炎患者は年間10人未満で推移し，地域別にみると毎年8～10月にかけて九州，中国・四国地方に患者が多い．ウイルスの増幅動物であるブタの日本脳炎感染率も同様の分布を示す[1]．つまり脳炎患者は少ないが，ウイルス自体は依然として存在しているので日本脳炎の脅威は

残っている.

Ⅱ 積極的勧奨の差し控えとその影響

2005年5月に日本脳炎ワクチン第3期接種後の重症なADEMの症例が被害として認定されたことを受け，乾燥細胞培養日本脳炎ワクチン（細胞培養ワクチン）の供給体制が整うまで積極的勧奨が控えられることになった．この結果，定期接種であることに変わりはなかったが，80%を超えていた第1期初回のワクチン実施率が2006年には約5%に低下し，細胞培養ワクチンの登場まで低い実施率が続いた.

2012年度の年齢/年齢群別の日本脳炎抗体保有状況[2]によると，積極的勧奨の差し控えによって低下した小児の抗体保有率は，2010年度からの接種勧奨の再開により徐々に上昇し，勧奨差し控え前に戻りつつある（**図1**）．また，20歳代までは比較的高い抗体陽性率を維持しているが，その後は低下し，中高年で従来から抗体保有率の低下が顕著にみられる．これについては，該当世代の20〜30年前の同調査で約80%の人が抗体を有していたので，小児期のワクチン接種で獲得した抗体価が，経時的に低下したのではないかと考えられる.

また，近年の自然感染率の低下のためか，若い年齢層では抗体陽性率の低下が早まっている．また世代間で事情は異なっているものの，小児から成人のおよそ20%がわが国では日本脳炎ウイルスに対する免疫をまったくもたない感受性者であると推測される．年間10人未満の日本脳炎患者はこのような状況の中で発生しており，ワクチン接種の積極的勧奨を差し控えていた2005年から2011年の7年間に，熊本，高知，山口，沖縄，福岡各県で計6例の小児の日本脳炎患者が報告された.

Ⅲ 乾燥細胞培養日本脳炎ワクチン

新しい細胞培養ワクチンは，従来のマウス脳由来ワクチンと同様，北京株ウイルスをVero細胞（アフリカミドリザル腎臓由来の株化細胞）で増殖させ，培養液からウイルスを回収して濃縮し，ホルマリンで不活化したものである．凍結乾燥品なので製剤的に長期に安定で，チメロサールなどの保存剤は含有しない.

① 未知の感染性因子の混入リスクの低減，② 安定供給，③ 動物愛護の観点，④ ADEM発症の「理論的懸念」を軽減などが開発のコンセプトであった．また，種ウイルス（北京株）とVero細胞はシードロットシステムによる品質管理が行われている[3].

細胞培養ワクチンは，マウス脳由来ワクチンにくらべて少ない抗原量で良好な抗体価が得られており，免疫原性がよい．臨床試験における中和抗体価の推移などをみても，初回免疫として2回接種を行い，さらにおおむね1年後に1回追加接種することにより十分な基礎免疫が得られている（**図2**）.

第2期の追加接種の臨床研究では，第1期に細胞培養ワクチンを接種した群，およびマウス脳由来ワクチンを接種した群に対し，おおむね7年後に第2期として細胞培養ワクチンを1回接種して前後の抗体価を測定したところ，追加免疫効果がみられ，1期3回接種後の抗体レベルまでに再上昇した（**図3**）．副反応の多くは接種部位の発赤，腫脹などの局所反応で，重篤な副反応はなかった.

Ⅳ 日本脳炎に関する小委員会

2009年6月に発売された細胞培養ワクチン（ジェービックV®）は，同時に第1期定期接種への使用が認められた．同年12月には厚生科学審議会の感染症分科会予防接種部会に「日本

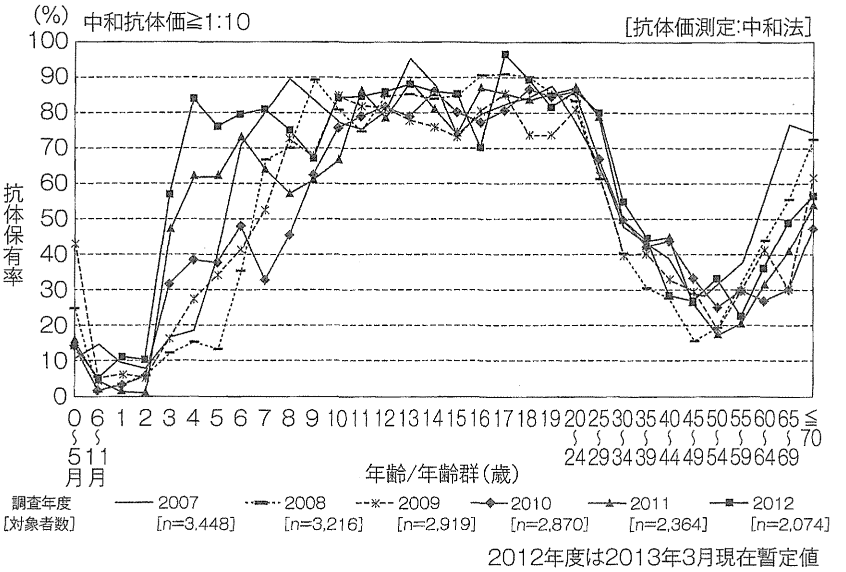
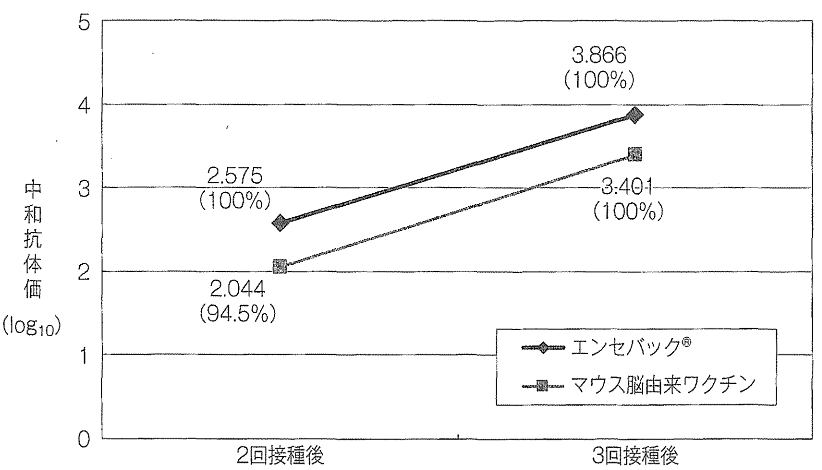


図1　年齢/年齢群別の日本脳炎抗体保有状況の年度比較，2007～2012年
（文献2）より引用）



	2回接種後		3回接種後	
	抗体陽転率	中和抗体価(log_{10})*	抗体陽転率	中和抗体価(log_{10})*
エンセバック®	100% (143/143)	2.575 (376)	100% (143/143)	3.866 (7,345)
マウス脳由来ワクチン	94.5% (138/146)	2.044 (111)	100% (146/146)	3.401 (2,518)

*：日本脳炎の感染防御に必要な中和抗体価は10倍以上

図2　乾燥細胞培養日本脳炎ワクチンの第3相臨床成績（文献4）より引用）

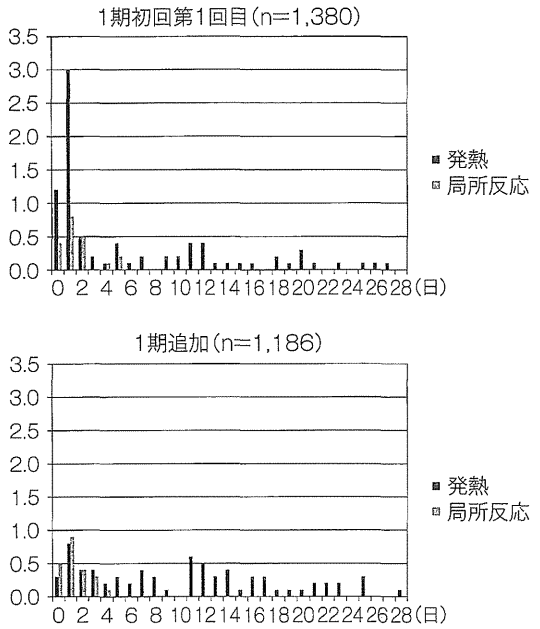


図6　日本脳炎ワクチン接種後健康状況調査（平成23年度）（文献7）より引用）

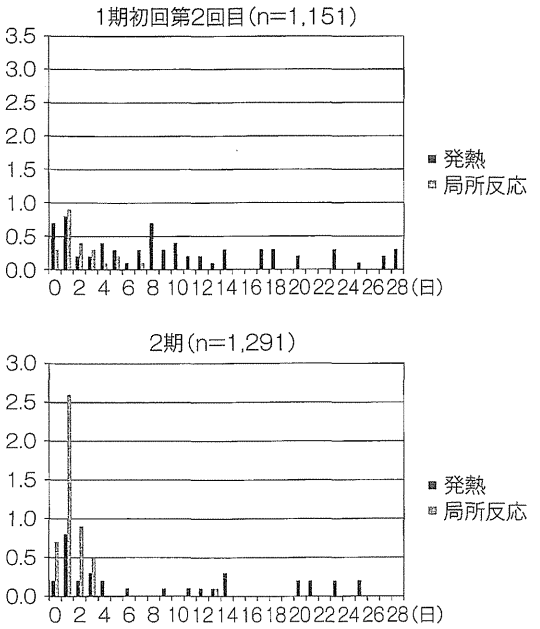


図7　日本脳炎ワクチン接種後健康状況調査（平成23年度）（文献7）より引用）

勧奨の差し控えにより接種機会を逃した者として政令改正の対象になった特例対象者は，前述のように20歳未満まで定期接種が可能である（**図5**）．

日本脳炎ワクチンの接種間隔や回数を考えるうえでの要点は，接種間隔より接種回数を重視し，最低3回の接種を行って基礎免疫をつけることをまず考え，一定間隔をあけて第2期接種（4回目）を行う．

1期初回の接種の間隔や，不規則接種になった場合の接種間隔は最低6日以上とされているが，免疫効果を考えると規定の範囲内で間隔が広くあいたほうがより効果的である．1期の追加接種まで計3回の接種を行うと高い中和抗体を得ることができるので，2期接種は5年以上間隔をあけても抗体が維持され，かつ追加免疫効果も十分期待できる．間隔が広くあいたからといって，最初から接種をやり直す必要はなく，規定の回数を接種する．ただし，間隔をあけすぎると接種を忘れてしまう危険もあるので，要注意である．

なお，細かい内容は，厚生労働省作成のQ＆Aなどに詳しく載っているのでご参照いただきたい[6]．

Ⅵ 細胞培養ワクチンの副反応と安全性

市販された2つの細胞培養ワクチンの主な副反応としては発熱，注射部位の紅斑，腫脹，発疹などがみられる．第3相試験および市販直後調査の結果や予防接種後健康状況調査[7]では，接種後3日以内の発熱が数％みられた．マウス脳由来ワクチンにくらべて1回目の接種後のみ発熱率がやや高いが，2回目以降では発熱率そのものが低く，局所反応はむしろ軽い傾向にある（**図6，7**）．

2012年秋に細胞培養ワクチン接種後の2人の死亡例やADEM症例が報告され，日本脳炎に関する小委員会で因果関係等が審議された．死亡例とワクチン接種の直接的因果関係は認め

表　乾燥細胞培養日本脳炎ワクチンでの ADEM 報告頻度

副反応報告と薬事法に基づく報告の合計：2009（平成 21）年 6 月～2010（平成 24）年 9 月

	報告数	接種回数	発生頻度
2009（平成 21）年度	0	1, 526, 771	0
2010（平成 22）年度	3	4, 367, 716	146 万回接種に 1 例
2011（平成 23）年度	7	5, 611, 321（推定）	80 万回接種に 1 例
2012（平成 24）年度（9 月末）	1	2, 945, 263（推定）	295 万回接種に 1 例
合計	11	14, 451, 071（推定）	131 万回接種に 1 例
備考	・副反応報告と薬事法に基づく報告を併せた数 ・接種日を基準に分類 ・重複例，取り下げ例を除く	・平成 21 年度は旧ワクチンの実績（2 カ月分）を含む ・平成 23 年度および平成 24 年度（9 月末まで）は，平成 22 年度の出荷量と被接種者数の比を用いて計算した数値	

（参考）旧ワクチンでの ADEM 報告頻度：70～200 万回接種に 1 例程度
（文献 10）より引用）

られないとされた．また ADEM 症例の発症頻度（表）も旧ワクチンや国際的なデータにくらべて高くなく，現在までの副反応の状況をもって日本脳炎ワクチンによる接種者の健康被害のリスクが高まったわけではないとされた[6]．一方で，日本脳炎ウイルスは現在のわが国でも依然脅威であり，予防接種を中止した場合には日本脳炎に罹患したり，重症化したり，死亡したりする事例が現在よりも多く発生する可能性が高いことも報告され，審議の結果，これまで同様接種勧奨は継続されるべきとされた．

日本脳炎ワクチンと ADEM の関係を考えると，幾度も改良を重ねていたマウス脳由来ワクチンは最終的に非常に高度に精製されていたので，脳由来であるがゆえに ADEM 発症の頻度が高くなるとは，理論的にも考えにくかった．実際に，わが国の小児の ADEM の発症頻度調査では，積極的勧奨が行われていた 2003～2004 年の 2 年間と，勧奨差控え後の 2005～2006 年の 2 年間では小児人口 10 万あたりの発生頻度は 0.33 と 0.34 でほぼ同等であった．ADEM の原因は多岐にわたっており，細胞培養ワクチンであっても偶然による紛れ込みも含めて接種後一定期間内の ADEM は起こりうると考えられる[3]．

Ⅶ 海外の状況

海外では，中国，極東，東南アジア，インド，ネパールなどで，年間数万人の日本脳炎患者の発生がみられている．日本，韓国，台湾，最近の中国など，ワクチンを導入した国では患者が激減または減少しているが，ワクチンを定期接種していない国ではむしろ増加している[8]．これはワクチン効果を示す事象と思われるが，いずれの国々でも日本と同様にウイルスとその媒介蚊は常在しているので，患者数が多い国（または調査できていない国）のみならず，減少した地域に渡航する時にも予防接種が重要である．

日本脳炎の危険性がある地域へ行く場合，これまでワクチン接種をしていなければ出国までに 2 回の予防接種とさらにおおむね 1 年後の接種により基礎免疫を獲得するようにし，十分な接種歴（基礎免疫）があるならば 1 回追加接種することを検討するのがよい．

米国では日本製のマウス脳由来ワクチンが使用されていたが，日本が製造を中止したため欧州製のアジュバントを加えた細胞培養ワクチンが認可された[9]．中国では生ワクチンが使用され患者数が減少しているが，安全性の確認が十分ではない．日本で新しく開発された細胞培養ワクチンはアジュバントを含まない不活化ワクチンで，免疫原性もよく，高度に精製されており安全性も高いと思われる．

おわりに

日本脳炎ウイルスはなお広く蔓延している．わが国で開発された細胞培養ワクチンは高い抗原性がある．積極的勧奨が再開され，小児期の免疫ギャップは解消されつつある．今後も副反応に注意しながら接種を進めて症例をなくしていきたいが，抗体陽性率が低い中高年対策はなお残された課題である．

文献

1) 国立感染症研究所ウイルス第1部：日本脳炎疾患情報
http://www.nih.go.jp/niid/ja/diseases/na/je.html
2) 国立感染症研究所感染症疫学センター：感染症流行予測調査2012年度
http://www.nih.go.jp/niid/ja/y-graphs/3505-je-yosoku-year2012.html
3) 宮崎千明：日本脳炎ワクチン―乾燥細胞培養日本脳炎ワクチンと接種勧奨の再開．医学のあゆみ 2013；244：79-85
4) エンセバック®審査報告書：23-24
http://www.info.pmda.go.jp/shinyaku/P201100014/20001100_22300AMX00412_A100_1.pdf
5) 岡田賢司ほか：「乾燥細胞培養日本脳炎ワクチン（エンセバック®皮下注用）第2期接種における安全性，有効性に関する臨床研究」厚生労働科学研究補助金　新型インフルエンザ等新興・再興感染症研究事業（平成24年3月）：52-64
6) 厚生労働省：日本脳炎ワクチン接種に係るQ＆A（平成25年3月改訂版）
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/nouen_qa.html
7) 予防接種副反応・健康状況調査検討会，厚生労働省健康局結核感染症課：予防接種後健康状況調査集計報告書（平成23年度後期分および累計分）
http://www.mhlw.go.jp/stf/shingi/2r9852000002qfxs-att/2r9852000002qfz9.pdf
8) Cambell G et al：Estimated global incidence of Japanese encephalitis：a systematic review. Bull WHO 2011；89：766-774E
9) Fischer M et al（CDC）：Japanese encephalitis vaccines：recommendations of the Advisory Committee on Immunization Practices（ACIP）. MMWR Recomm Rep 2010；59：1-27
10) 厚生労働省：第7回厚生科学審議会感染症分科会予防接種部会日本脳炎に関する小委員会，資料2 新ワクチンでのADEM報告頻度（2013年1月31日現在）
http://www.mhlw.go.jp/stf/shingi/2r9852000002ndoo-att/2r9852000002ndr5.pdf

Clinical and Vaccine Immunology

Immunogenicity and Safety after Booster Vaccination of Diphtheria, Tetanus, and Acellular Pertussis in Young Adults: an Open Randomized Controlled Trial in Japan

Megumi Hara, Kenji Okada, Yuko Yamaguchi, Shingo Uno, Yasuko Otsuka, Chisato Shimanoe, Hinako Nanri, Mikako Horita, Iwata Ozaki, Yuichiro Nishida and Keitaro Tanaka

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Immunogenicity and Safety after Booster Vaccination of Diphtheria, Tetanus, and Acellular Pertussis in Young Adults: an Open Randomized Controlled Trial in Japan

Megumi Hara,[a] Kenji Okada,[b] Yuko Yamaguchi,[c] Shingo Uno,[c] Yasuko Otsuka,[a] Chisato Shimanoe,[a] Hinako Nanri,[a] Mikako Horita,[a] Iwata Ozaki,[d] Yuichiro Nishida,[a] Keitaro Tanaka[a]

Department of Preventive Medicine, Faculty of Medicine, Saga University, Saga City, Japan[a]; Department of Pediatrics, Fukuoka Dental College, Fukuoka City, Fukuoka, Japan[b]; The Chemo-Sero-Therapeutic Research Institute (Kaketsuken), Kumamoto City, Kumamoto, Japan[c]; Health Care Center, Saga University, Saga City, Saga, Japan[d]

The recent increase of pertussis in young adults in Japan is hypothesized to be due in part to waning protection from the acellular pertussis vaccine. While a booster immunization may prevent an epidemic of pertussis among these young adults, little is known about the safety and immunogenicity of such a booster with the diphtheria, tetanus, and acellular pertussis vaccine (DTaP), which is currently available in Japan. One hundred and eleven medical students with a mean age of 19.4 years were randomly divided into 2 groups of 55 and 56 subjects and received, respectively, 0.2 or 0.5 ml of DTaP. Immunogenicity was assessed by performing the immunoassay using serum, and the geometric mean concentration (GMC), GMC ratio (GMCR), seropositive rate, and booster response rate were calculated. Adverse reactions and adverse events were monitored for 7 days after vaccination. After booster vaccination in the two groups, significant increases were found in the antibodies against pertussis toxin, filamentous hemagglutinin, diphtheria toxoid, and tetanus toxoid, and the booster response rates for all subjects reached 100%. The GMCs and GMCRs against all antigens were significantly higher in the 0.5-ml group than in the 0.2-ml group. No serious adverse events were observed. Frequencies of local reactions were similar in the 2 groups, although the frequency of severe local swelling was significantly higher in the 0.5-ml group. These data support the acceptability of booster immunization using both 0.2 and 0.5 ml of DTaP for young adults for controlling pertussis. (This study was registered at UMIN-CTR under registration number UMIN000010672.)

During the last few decades, the number of reported pertussis cases has increased in developed countries, despite high vaccination coverage (1). This resurgence of reported pertussis has been hypothesized to be due to several reasons, including increased awareness of pertussis; use of PCR assay for diagnosis; failure of the diphtheria, tetanus, and acellular pertussis vaccine (DTaP); and genetic changes in circulating strains of *Bordetella pertussis* (2, 3). DTaP does not confer lifelong immunity, and it has been reported to last for 4 to 12 years after infant immunization (4). A recent study demonstrated that after the fifth dose of DTaP, protection against pertussis waned during the following 5 years, and the risk of pertussis increased by an average of 42% per year (5).

The prevalence of pertussis in Japan was estimated to be 2.4 (95% confidence interval, 1.6 to 3.3) per 100,000 population in 2007 (see the National Institute of Infectious Diseases fact sheet for pertussis vaccine [in Japanese] at http://www.mhlw.go.jp/stf/shingi/2r9852000000bx23-att/2r9852000000byfg.pdf), while the prevalence in the United States was reported to be 9.0 per 100,000 population in 2010 (3). It is difficult to compare these values, because of differences of diagnostic methods applied and case definitions for surveillance. However, the proportion of adults among recently reported pertussis cases has been increasing in Japan (see the National Institute of Infectious Diseases fact sheet), even though underreporting of adult cases was suspected due to the fact that pertussis cases were primarily reported from pediatric clinics. In Japan, children receive 4 doses of the DTaP vaccine, with 3 primary doses and a single booster dose at ages 3, 4, 5, and 18 to 23 months. Thus, a decreased protective effect of the vaccine may contribute to the increasing frequency of pertussis in the last decade on college campuses and in high schools and offices in Japan (6–10). Pertussis prevention among young adults is important because unrecognized adult pertussis is the major source of pertussis in young infants, in whom the disease can be severe and fatal (2).

The tetanus, reduced antigen content diphtheria, and acellular pertussis vaccine (Tdap) is used as a booster vaccination worldwide for adults, and its effects in adolescents and adults, as well as in specific risk groups, such as pregnant women and their newborns, health care workers, and older adults, have been reported (11–13). Since Tdap has not yet been licensed in Japan, DTaP may be available for booster immunization in the interim. Safe and effective booster immunization using DTaP in adolescents has been confirmed (14); however, little is known about the immunogenicity and safety of the DTaP vaccine in young adults. In this study, we examined the immunogenicity and safety of 0.2 and 0.5 ml of DTaP in young adults in Japan.

MATERIALS AND METHODS

Study subjects and design. The participants were recruited at the Saga University, located in southern Japan, where an outbreak of pertussis had

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Address correspondence to Megumi Hara, harameg@cc.saga-u.ac.jp.

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occurred among medical students during April and May in 2010. After the outbreak, we used an enzyme-linked immunosorbent assay (ELISA) at a commercial laboratory (SRL, Tokyo) to examine antibodies against pertussis toxin (PT) in all 548 students during July and August 2010. We found that the levels of antibodies against PT among 258 students (47%) were <10 ELISA units (EU)/ml, and those among 24 students (4%) were ≥100 EU/ml. We announced the participation of these students in this study during August 2011. Students were excluded from participation if their antibody levels against PT were ≥100 EU/ml in 2010; if they had any history of diphtheria, tetanus, and pertussis; if they had received any other drug or vaccine within 30 days of entry; if they had a history of allergic reactions to any vaccine component; or if they had received immunoglobulins or any blood products. Subjects were also excluded if they had acute disease or febrile illness at the time of vaccination. Overall, 111 students aged 19 to 20 years participated in this study. They had undergone primary vaccination with the DTaP vaccine in Japan during childhood. The immunization histories of 83 subjects were confirmed by checking their immunization records, whereas those of the remaining 28 subjects could not be verified because they did not submit their records.

This study (registered at UMIN-CTR under registration number UMIN000010672) was an open randomized controlled trial performed using blocked randomization for gender and prevaccination antibody levels against PT. The study subjects were stratified according to seropositivity for PT (PT-IgG, ≥10 EU/ml) or nonseropositivity for PT (PT-IgG, <10 EU/ml) in the previous year, and according to gender. Then, the subjects within each group were randomly assigned to receive 0.2 or 0.5 ml of DTaP vaccine. Serum samples were obtained before immunization and 1 month after immunization. All serum specimens were stored at −80°C until assayed. All subjects were included in the safety and immunogenicity analysis.

The study was conducted in accordance with good clinical practice guidelines and the principles of the Declaration of Helsinki and Japanese regulatory requirements. The study protocol was approved by the Institutional Review Board of the Saga University Faculty of Medicine (approval number 23-14, 2011). The nature and possible consequences of the study were discussed at length with all subjects, and written informed consent for participation was obtained from all.

Vaccines. The single doses of 0.2 and 0.5 ml of adsorbed diphtheria-purified pertussis-tetanus combined vaccine (DTaP vaccine, lot number 42A; Kaketsuken) contained 3.2 and 8 μg of PT, 12.8 and 32 μg of filamentous hemagglutinin (FHA), ≤6.7 and ≤16.7 Lf of diphtheria toxoid (D), and ≤2.7 and ≤6.7 Lf of tetanus toxoid (T), respectively. This DTaP also contained 0.004 mg/ml of thimerosal, <3 mg/ml of aluminum hydroxide, and <1 mg/ml of formalin. The vaccine was administered subcutaneously in the lateral upper arm by using a 27-gauge needle of length 25 mm.

Assessment of safety. All subjects were carefully observed for anaphylactic shock for at least 30 min after vaccination. To assess for adverse reactions occurring during the initial 24 h and the 7 days immediately following vaccination, the subjects were asked to perform daily self-assessments and record their body temperature at the axillary fossa and their adverse reactions based on a standard health care diary. Adverse reactions occurring within 24 h included the following: fever (temperature of ≥38.0°C), eye hyperemia, facial edema, cough, dyspnea, dysphasia, hoarseness, and sore throat. After 24 h, the adverse local symptoms consisted of erythema, swelling, pain, warmth, and pruritus, whereas systemic reactions included fever (temperature of ≥38.0°C), headache, fatigue, cough, and sore throat. The degrees of erythema and swelling in the local reactions were evaluated by the diameter of the swelling and were defined as follows: mild (<2.0 cm), moderate (2.0 to 4.9 cm), and severe (≥5.0 cm). The degrees of pain, warmth, and pruritus in local reactions were also categorized based on the patients' perceptions and defined as follows: mild, if the patient was aware of the reaction but not concerned; moderate, if the patient was anxious; and severe, if the patient required medication for pain and/or pruritus. All subjects were monitored for 6 months after vaccination to get the maximum information regarding unexpected serious adverse events.

Serological assays. Serum antibodies against PT, FHA, D, and T were concurrently measured by Kaketsuken. Antibodies to PT and FHA were measured using standard enzyme-linked immunosorbent assays (ELISA), and pertussis antibody titers were expressed as ELISA units (EU)/ml (15). Diphtheria antitoxin titers were examined using the micro cell culture method with Vero cells and expressed as international units (IU)/ml (16). Tetanus antitoxin titers were determined using a KPA kit (Kaketsuken, Japan) and expressed as international units (IU)/ml (17). Limits of quantification for each antibody against PT, FHA, D, and T were 1.0 EU/ml, 1.0 EU/ml, 0.005 IU/ml, and 0.005 IU/ml, respectively. Seropositive levels were defined as ≥10 EU/ml for antibodies against PT and FHA, ≥0.1 IU/ml for diphtheria antitoxin, and ≥0.01 IU/ml for tetanus antitoxin (14). A booster response for PT and FHA was defined as a postvaccination antibody concentration of ≥20 EU/ml with a prevaccination antibody concentration of <5.0 EU/ml, a postvaccination rise of at least 4 times the prevaccination antibody concentration in subjects with a prevaccination antibody concentration of 5.0 to 20 EU/ml, or at least twice the prevaccination antibody concentration in subjects with a prevaccination antibody concentration of ≥20 EU/ml. Booster responses for D and T were defined as a postvaccination antibody concentration of ≥0.4 IU/ml with a prevaccination antibody concentration of <0.1 IU/ml, or a postvaccination increase of at least 4 times the prevaccination antibody concentration with an initial concentration of ≥0.1 IU/ml (18).

Statistical analyses. The primary objective of the study was to demonstrate booster response rates of at least 80% for PT, FHA, D, and T in the two groups. The chi-square test or Fisher's exact test was used to compare the baseline characteristics or seropositivity rates and frequency of adverse reactions between the groups. The 95% confidence interval (CI) of seropositivity rates were calculated with the exact binomial distribution for proportions. Because distributions of antibodies were skewed, all antibody calculations were done using a log scale. The Wilcoxon rank-sum test was used to compare the GMC and GMC ratio (GMCR) between the 2 groups, while the Wilcoxon signed-rank test was used to determine the significance of the increase in antibodies after vaccination in each group. Hypothesis testing was conducted using two-sided tests, with an α value of 0.05 considered statistically significant. All statistical analyses were performed using the SAS software (version 9.1).

RESULTS

Baseline characteristics of the subjects. Baseline demographic characteristics of the 2 groups are shown in Table 1. There were no statistical differences between the 2 groups in the proportions of female subjects, age distributions, DTaP histories, current diseases, and allergy histories. Furthermore, the distributions of prevaccination antibodies and seropositivity rates before vaccination against PT, FHA, D, and T were similar in the 2 groups (Table 2).

Immunogenicity. After each DTaP vaccination, each group demonstrated significant increases in the GMC and GMCR of antibodies and seropositivity rates against PT, FHA, D, and T (Table 2). The immune responses were significantly lower in the 0.2-ml group than in the 0.5-ml group; however, both groups reached 100% seropositivity and booster response rates against all antigens. These results satisfied our primary objectives.

Safety. No serious adverse events occurred during the study period. Several adverse reactions occurred, but all were transient and occurred at similar frequencies in the 2 groups (Table 3). Within 24 h after vaccination, the most frequent symptoms were cough (3.6%), dysphasia (3.6%), and sore throat (3.6%). After 24 h, local reactions were frequently observed, with few systemic reactions. The onset of local reactions is summarized in

TABLE 1 Baseline characteristics of the study subjects

Characteristic	Values for subjects who received: 0.2 ml DTaP (n = 55)	0.5 ml DTaP (n = 56)	P^a
Female (n [%])	42 (76.4)	41 (73.2)	0.703
Age (mean ± SD) (yr)	19.4 ± 1.2	19.4 ± 0.8	0.97
DTP history (n [%])			
1 dose	1 (1.8)	0 (0)	0.617
3 doses	2 (3.9)	2 (3.9)	
4 doses	33 (63.5)	37 (72.6)	
Uncertain	16 (30.8)	12 (23.5)	
Disease (n [%])			
Asthma	1 (1.8)	0 (0)	0.496
Atopic dermatitis	2 (3.6)	2 (3.6)	1
Allergy history (n [%])			
Drugs	3 (5.4)	2 (3.6)	0.679
Foods	7 (12.7)	3 (5.4)	0.202

[a] P values were tested by the t, chi-square, or Fisher's exact test.

TABLE 3 Adverse reactions after vaccination

Time span and adverse reaction	No. (%) of subjects with adverse reaction to: 0.2 ml DTaP (n = 55)	0.5 ml DTaP (n = 56)	P^a
Within 24 h			
Fever (≥38.0°C)	0 (0)	1 (1.8)	1.000
Eye hyperemia	0 (0)	1 (1.8)	1.000
Face edema	0 (0)	1 (1.8)	1.000
Cough	2 (3.6)	2 (3.6)	1.000
Dyspnea	0 (0)	1 (1.8)	1.000
Dysphasia	0 (0)	2 (3.6)	0.495
Hoarseness	0 (0)	1 (1.8)	1.000
Sore throat	1 (1.8)	2 (3.6)	1.000
After 24 h			
Local reaction			
Erythema	39 (70.9)	33 (58.9)	0.186
Swelling	33 (60.0)	33 (58.9)	0.908
Pain	34 (61.8)	38 (67.9)	0.505
Hotness	23 (41.8)	27 (48.2)	0.444
Itching	27 (49.1)	25 (44.6)	0.639
Systemic reaction			
Fever (≥38.0°C)	0 (0)	1 (1.8)	1.000
Headache	0 (0)	2 (3.6)	0.495
Fatigue	3 (5.5)	2 (3.6)	0.679
Cough	1 (1.8)	2 (3.6)	1.000
Sore throat	2 (3.8)	1 (1.8)	0.618

[a] P values were tested by Fisher's exact test or chi-square test.

Table 4. Erythema, swelling, and pain were reported by more than half of the subjects. Most injection site reactions resolved within 3 days.

The severities of the local reactions are summarized in Table 5. The frequencies of severe local reactions tended to be higher in the 0.5-ml group than in the 0.2-ml group. Moreover, the frequency of local swelling was significantly higher in the 0.5-ml group than in the 0.2-ml group (relative risk [RR], 4.42; 95% CI, 1.00 to 19.54). However, none of these reactions affected the subjects' ordinary daily activities.

DISCUSSION

In this randomized clinical trial comparing 0.2 ml to 0.5 ml of DTaP vaccine in young adults, we showed that effective immunogenicity for PT, FHA, D, and T was achieved in both groups. All

TABLE 2 Antibody GMCs, seropositive levels, and booster responses after DTaP vaccinations[d]

Antibody	Dose (ml)	n	GMC concn (per ml [95% CI]) Prevaccination	Postvaccination	GMCR	P^b	No. (%) (95% CI) of subjects who were seropositive[e] Prevaccination	Postvaccination	No. (%) (95% CI) of subjects with a booster response[f]
Anti-PT	0.2	55	7.81 (5.31, 11.49) EU	90.90 (73.95, 111.74) EU	11.6	<0.0001	23 (42) (29, 56)	55 (100) (94, 100)	55 (100) (94, 100)
	0.5	56	6.83 (4.97, 9.40) EU	168.71 (141.93, 200.54) EU	24.7	<0.0001	21 (38) (25, 52)	56 (100) (94, 100)	56 (100) (94, 100)
P			0.6205[a]	<0.0001[a]	<0.001[a]		0.6434[c]	NC	NC
Anti-FHA	0.2	55	24.39 (16.76, 35.51) EU	213.36 (177.63, 256.26) EU	8.7	<0.0001	43 (78) (67, 88)	55 (100) (94, 100)	55 (100) (94, 100)
	0.5	56	20.71 (15.48, 27.72) EU	397.77 (333.80, 474.00) EU	19.2	<0.0001	40 (71) (58, 52)	56 (100) (94, 100)	56 (100) (94, 100)
P			0.4951[a]	<0.0001[a]	<0.001[a]		0.4148[c]	NC	NC
Anti-D	0.2	55	0.22 (0.16, 0.30) IU	4.29 (3.53, 5.21) IU	19.8	<0.0001	41 (75) (63, 86)	55 (100) (94, 100)	55 (100) (94, 100)
	0.5	56	0.21 (0.15, 0.30) IU	6.28 (4.86, 8.11) IU	30.1	<0.0001	39 (70) (56, 81)	56 (100) (94, 100)	56 (100) (94, 100)
P			0.9016[a]	0.0109[a]	0.01[a]		0.5666[c]	NC	NC
Anti-T	0.2	55	0.25 (0.18, 0.34) IU	1.46 (1.26, 1.69) IU	5.9	<0.0001	55 (100) (94, 100)	55 (100) (94, 100)	55 (100) (94, 100)
	0.5	56	0.27 (0.21, 0.35) IU	2.52 (2.14, 2.96) IU	9.4	<0.0001	56 (100) (94, 100)	56 (100) (94, 100)	56 (100) (94, 100)
P			0.9112[a]	<0.0001[a]	<0.001[a]		NC	NC	NC

[a] P values were calculated between groups by using the Wilcoxon rank-sum test with a log scale of antibodies.

[b] P values were calculated between prevaccination and postvaccination by using the Wilcoxon signed-rank test with a log scale of antibodies.

[c] P values were calculated between groups by using the chi-square test.

[d] CI, confidence interval; GMC, geometric mean concentration; GMCR, ratio of GMC of prevaccination to postvaccination; NC, not compared.

[e] Seropositive levels were defined as ≥10 EU/ml for antibodies against PT and FHA, ≥0.1 IU/ml for those against diphtheria toxoid, and ≥0.01 IU/ml for those against tetanus toxoid.

[f] Booster responses for PT and FHA were defined as postvaccination antibody concentrations of ≥20 EU/ml with a prevaccination antibody concentration of <5.0 EU/ml, a postvaccination rise of at least 4 times the prevaccination antibody concentration in subjects with a prevaccination antibody concentration of 5.0 to 20 EU/ml, or at least twice the prevaccination antibody concentration in subjects with a prevaccination antibody concentration of ≥20 EL U/ml. Booster responses for D and T were defined as a postvaccination antibody concentration of ≥0.4 IU/ml with a prevaccination antibody concentration of <0.1 IU/ml or a postvaccination increase of at least 4 times the prevaccination antibody concentration with an initial concentration of ≥0.1 IU/ml.

TABLE 4 Onset of local reactions

Local reaction	Vaccine dose (ml)	No. (%) of subjects with indicated local reaction: Day of onset 0	1	2	3	4	5	6	7	Total no. (%) with indicated reaction
Erythema	0.2	10 (18.2)	14 (25.5)	11 (20.0)	3 (5.5)	0	0	1 (1.8)	0	39 (70.9)
	0.5	9 (16.1)	14 (25.0)	8 (14.3)	1 (1.8)	0	1 (1.8)	0	0	33 (58.9)
Swelling	0.2	6 (10.9)	15 (27.3)	9 (16.4)	2 (3.6)	0	1 (1.8)	0	0	33 (60.0)
	0.5	8 (14.3)	15 (26.8)	8 (14.3)	2 (3.6)	0	0	0	0	33 (58.9)
Pain	0.2	11 (20.0)	14 (25.5)	7 (12.7)	2 (3.6)	0	0	0	0	34 (61.8)
	0.5	15 (26.8)	17 (30.4)	5 (8.9)	1 (1.8)	0	0	0	0	38 (67.9)
Hotness	0.2	7 (12.7)	10 (18.2)	4 (7.3)	2 (3.6)	0	0	0	0	23 (41.8)
	0.5	8 (14.3)	8 (14.3)	10 (17.9)	1 (1.8)	0	0	0	0	27 (48.2)
Itching	0.2	8 (14.5)	10 (18.2)	4 (7.3)	2 (3.6)	2 (3.6)	1 (1.8)	0	0	27 (49.1)
	0.5	6 (10.7)	12 (21.4)	6 (10.7)	0	1 (1.8)	0	0	0	25 (44.6)

subjects in the two groups demonstrated sufficient booster responses against all vaccine antigens. None of the severe adverse reactions observed required medications. The total number and onset of local and systemic reactions between the 2 groups were similar, although the frequency of severe local swelling was significantly higher in the 0.5-ml group ($P < 0.05$). Thus, both doses of DTaP may provide adequate booster immunization in young adults in Japan, where the Tdap vaccine has not yet been licensed.

Clinical trials evaluating the duration of protective immunity provided by 3 or 4 doses of DTaP against pertussis demonstrated that protective immunity was sustained for 5 to 6 years after immunization (19, 20). The immunization schedule of DTaP in Japan consists of 4 doses in young children during 4 to 23 months of age and 1 dose of DT during 11 and 12 years of age. Thus, in our study participants, 17 to 18 years had elapsed since their last immunization. In our study, the prevaccination antibody seropositivity rates against pertussis were around 40% for PT and 70 to 80% for FHA, which are lower than those reported in Japanese adolescents (14) and Finnish young adults (21). In the former study, seropositivity rates against pertussis were 52 to 59% for PT and 79 to 86% for FHA among the adolescents, who were immunized for pertussis about 10 years prior (14). In the latter study, seropositivity rates at 10 years after the fifth dose of Tdap were 61.3% for PT and 100% for FHA (21).

Since immunogenicity to vaccination is influenced by the prevaccination antibody level, vaccination history, doses of vaccine components, and laboratory where the antibodies were measured, it is difficult to compare immunogenicity between previous studies using Tdap and the present study. With regard to the prevaccination antibody level, we observed antibody levels against PT and FHA that were lower than those in previous studies (14, 21). Thus, immunogenicities in our subjects may have been lower than those of the previous studies if the components of the vaccine were the same. The 0.5 ml of DTaP vaccine (Kaketsuken) contains the same dose of PT and higher doses of FHA, D, and T than the Boostrix Tdap (13) and higher doses of PT, FHA, D, and T than

TABLE 5 Degrees of local reactions

Type of reaction[a]	Vaccine dose (ml)	No. (%) of subjects with: Absence of reaction	Reaction: Mild	Moderate	Severe	Risk ratio (95% CI)[b] for severe local reactions
Redness	0.2	16 (29)	5 (13)	26 (67)	8 (21)	1 (reference)
	0.5	23 (41)	5 (15)	17 (52)	11 (33)	1.35 (0.59–3.10)
Swelling	0.2	23 (42)	8 (24)	22 (67)	2 (6)	1 (reference)
	0.5	23 (41)	6 (18)	18 (55)	9 (27)	4.42 (1.00–19.54)
Pain	0.2	21 (38)	23 (68)	10 (29)	1 (3)	1 (reference)
	0.5	18 (32)	22 (58)	13 (34)	3 (8)	2.95 (0.32–27.47)
Warmth	0.2	32 (58)		20 (87)	3 (13)	1 (reference)
	0.5	29 (52)		21 (78)	6 (22)	1.96 (0.52–7.46)
Pruritus	0.2	28 (51)	14 (52)	12 (44)	1 (4)	1 (reference)
	0.5	31 (55)	6 (24)	16 (64)	3 (12)	2.95 (0.32–27.47)

[a] Degrees of redness and swelling: mild (<2.0 cm), moderate (2.0 to 4.9 cm), or severe (≥5.0 cm). Degrees of pain, warmth, and pruritus: mild (sensed, but not anxious about), moderate (anxious), or severe (needs medication).
[b] CI, confidence interval.