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Interim analysis of a randomized, open-label, parallel design study to compare the immunogenicity of simultaneous administration versus sequential administration of quadrivalent influenza vaccine and 23-valent polysaccharide pneumococcal vaccine

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Introduction

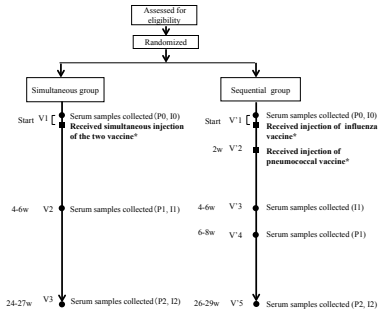
- Simultaneous administration of the influenza vaccine and pneumococcal vaccine can facilitate immunization against both pathogens, particularly in populations having difficulty reaching clinics and hospitals.
- In the 2015/2016 season, quadrivalent influenza vaccine was introduced in Japan instead of trivalent influenza vaccine.
- To determine whether simultaneous administration of influenza and pneumococcal vaccine is as safe and effective as administrating either vaccine alone, we compare the antibody response and adverse reactions in groups receiving the two vaccines simultaneously and individually.
- This is the first study to evaluate the immunogenicity and safety of simultaneous administration of quadrivalent influenza and 23-valent pneumococcal vaccines.

Methods

- Study Design
  Randomized, non-inferiority, open label trial was conducted at the Kameda Medical Center, Chiba, Japan, from October 2015 through August 2016.
- Hypotheses
  We hypothesized that the response rate (≥2-fold increase in IgG concentrations at 1month after administration of PPV23) of simultaneous administration of the two vaccines is not inferior to that of separate administration.

- Inclusion criteria
  - ✓ adults aged ≧65 years who had never received pneumococcal vaccine and quadrivalent influenza vaccine in the 2015/2016 season.
- Exclusion criteria
  - ✓ sensitivity to pneumococcal and influenza vaccine, received other inactivated vaccine within 14 days
  - ✓ presence of malignant disease
  - ✓ taking oral corticosteroids or immunosuppressive agent
  - ✓ history of splenectomy
  - ✓ history of an acute febrile illness
  - ✓ suffering an acute illness requiring antibiotics or steroids within the past month

Figure 1: study flowchart



*Pneumococcal vaccine: PPV23 (Pneumovax NP®, MSDKK, Tokyo, Japan)
Influenza vaccine: Quadrivalent influenza vaccine (Fluvic HA syringe®, Handai Biken Ltd, Osaka, Japan)

- Primary end point
  - ✓percentage of patients with positive antibody response in serotype 23F of pneumococcal antibody.
- Secondary end point
  - ✓positive antibody response in serotype 3, 4, 6B, 1 4 and 19A.
  - ✓geometric mean concentrations (GMC) of specific antibodies to the 6 serotypes (23F, 3, 4, 6B 14 and 19A) before vaccination (at baseline; in designated P0), 4 to 6 weeks after vaccination (P1), 24 weeks to 27 weeks after vaccination (P2)
  - ✓the percentage of patients with seroprotection rate (postvaccination titer >1:40) at 4 to 6 weeks after vaccination (I1) and 24 weeks to 27 weeks after vaccination (I2) in quadrivalent influenza vaccine.

- Statistical methods.

<Immunogenicity of pneumococcal vaccine>

- ✓ IgG antibody levels were transformed using natural logarithms for statistical analysis to account for their strongly skewed distributions and are reported as geometric means.
- ✓ Stratified analyses were performed to examine the effect of the following potential confounders: age at vaccination (<70 vs. ≥70); gender (male and female).
- ✓ Univariate and multivariate analysis were performed by logistic regression to determine the relationship between age and sex with vaccine responsiveness as measured by the number of serotypes to which a subject exhibited a 2-fold increase in IgG.

<Immunogenicity of influenza vaccine>

- ✓ The following outcomes were calculated to assess the immunogenicity of influenza vaccine: geometric mean titer GMT); fold-increase; seroprotection rate (postvaccination titer >1:40).
- ✓ Stratified analyses were performed to examine the effect of the following potential confounders: age at vaccination (<70 and ≥70 years); gender (male and female); prevaccination titer (<1:10, 1:10–1:20, and ≥1:40).
- ✓ The independent effects of potential confounders on antibody induction were evaluated by logistic regression. The models were constructed with seroprotection as the dependent variable and the above-mentioned potential confounders as explanatory variables. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. All tests were 2-sided.

<Safety>

- ✓ The proportion of subjects reporting systemic or local adverse reactions during 28 days were compared using Fisher exact test.

- This trial was registered with ClinicalTrials.gov, number NCT02592486.

Results

Figure 2: Consort Flow Diagram

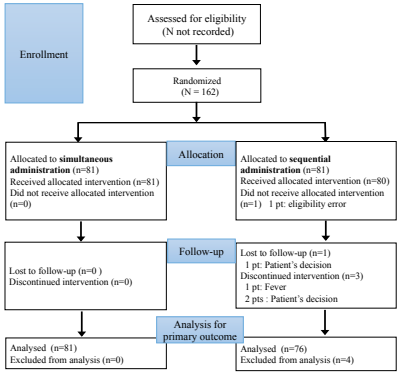


Table 1: Patient characteristics at allocation

	Simultaneous group N=81	Sequential group N=80
Age	71.0 (±5.1)	70.2 (±4.1)
Male	48 (59.3)	49 (61.3)
Last year influenza vaccination*	20 (25)	29 (36.7)
Previous history of pneumonia†	13 (16)	14 (17.7)
Previous history of influenza†	10 (12.3)	15 (19)
Underlying disease		
Chronic lung disease	54 (66.7)	54 (68.4)
Chronic heart disease	11 (14.8)	10 (12.7)
Hypertention	36 (44.4)	28 (35.4)
Diabetes	19 (23.8)	15 (19.2)
Dyslipidemia	36 (44.4)	24 (30.8)
Chronic renal disease	3 (3.7)	1 (1.3)
Cerebral vascular disorder	4 (5)	5 (6.3)
Neuromascular disease	0 (0)	1 (1.3)
Chronic liver disease	3 (3.7)	2 (2.6)

Data are expressed as number (%) of patients, unless otherwise indicated.
*Data of 2 cases are missing †Data of 1 case is missing

Figure 3: Difference in the response rate of 23F between the two groups

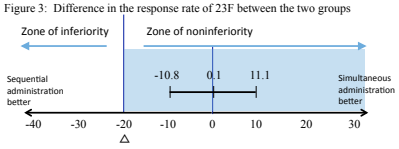


Table 2: Antibody to capsular polysaccharides.

Type, time point	Simultaneous group No	GMC	Sequential group No	GMC	*P* value
23F					
Before vaccination (P0)	81	0.40	80	0.20	<0.001
4-6weeks after vaccination (P1)	81	2.04	76	1.41	0.157
3					
Before vaccination (P0)	81	0.07	80	0.07	0.277
4-6weeks after vaccination (P1)	81	0.24	76	0.21	0.482
4					
Before vaccination (P0)	81	0.08	80	0.05	0.004
4-6weeks after vaccination (P1)	81	0.24	76	0.28	0.520
6B					
Before vaccination (P0)	81	0.24	80	0.14	0.007
4-6weeks after vaccination (P1)	81	0.96	76	0.96	0.993
14					
Before vaccination (P0)	81	0.68	80	0.42	0.032
4-6weeks after vaccination (P1)	81	2.78	76	4.72	0.070
19A					
Before vaccination (P0)	81	0.72	80	0.49	0.051
4-6weeks after vaccination (P1)	81	3.74	76	2.92	0.332

Note: Data are the geometric mean concentrations (GMC) of immunoglobulin G to each pneumococcal capsular polysaccharide, in μg/mL All changes within each group from P0 to P1 were statistically significant (P <0.001).

Table 3: Odds ratios for seroresponse rates of pneumococcal vaccination

Category	n/N	Crude analysis OR (95%CI)	*P* value	Multivariate analysis OR (95%CI)	*P* value
23F					
Sequential group	59/76 (77.6)	1	1.000	1	0.997
Simultaneous group	63/81 (77.8)	1.01(0.48-2.14)		1.00(0.47-2.13)	
3					
Sequential group	52/76 (68.4)	1	1.000	1	0.964
Simultaneous group	56/81 (69.1)	1.03(0.53-2.03)		1.02 (0.51-2.03)	
4					
Sequential group	66/76 (86.8)	1	0.004	1	0.003
Simultaneous group	54/81 (66.7)	0.30(0.14-0.68)		0.30 (0.13-0.67)	
6B					
Sequential group	63/76 (82.9)	1	0.179	1	0.130
Simultaneous group	59/81 (72.8)	0.55(0.26-1.20)		0.55 (0.25-1.20)	
14					
Sequential group	67/76 (88.2)	1	<0.001	1	<0.001
Simultaneous group	49/81 (60.5)	0.21(0.09-0.47)		0.20 (0.09-0.47)	
19A					
Sequential group	59/76 (77.6)	1	0.851	1	0.700
Simultaneous group	61/81 (75.3)	0.88(0.42-1.8)		0.86 (0.40-1.86)	

* Adjusted for age and gender

Table 4: Seroprotection rates of influenza vaccinations

Category	n/N	Crude analysis OR (95%CI)	*P* value	Multivariate analysis* OR (95%CI)	*P* value
H1N1					
Sequential group	60/77 (78)	1	0.418	1	0.156
Simultaneous group	68/81 (84)	1.48 (0.67-3.30)		1.9 (0.78-4.59)	
H3N2					
Sequential group	68/77 (88)	1	0.235	1	0.260
Simultaneous group	66/81 (82)	0.58 (0.24-1.42)		0.56 (0.21-1.52)	
B Texas					
Sequential group	45/77 (58)	1	0.038	1	0.021
Simultaneous group	33/81 (41)	0.49 (0.26-0.92)		0.46 (0.24-0.89)	
B Phuket					
Sequential group	48/77 (62)	1	0.871	1	0.840
Simultaneous group	49/81 (61)	0.93 (0.49-1.76)		0.93 (0.47-1.86)	

* Adjusted for age, gender and prevaccination titer

Table 5: Adverse events between the two groups

	Simultaneous group N=81	Sequential group N=76	*P* value
Systemic events			
fever*	2 (2.5)	3 (4.2)	0.668
fatigue	9 (11.2)	16 (21.2)	0.138
headache	4 (4.9)	5 (6.6)	0.740
joint pain	11 (13.6)	11 (14.5)	1.000
pain of axilla	4 (4.9)	4 (5.3)	1.000
rash	1 (1.2)	2 (2.6)	0.611
Local reactions			
pneumococcal vaccination			
induration	20 (24.7)	14 (18.4)	0.448
itch	16 (19.8)	12 (15.8)	0.660
pain	28 (34.6)	36 (47.4)	0.142
redness	23 (28.4)	19 (25)	0.764
swelling	24 (29.6)	13 (17.1)	0.097
Influenca vaccination			
induration	19 (23.5)	11 (14.5)	0.220
itch	18 (22.2)	14 (18.4)	0.695
pain	23 (28.4)	14 (18.4)	0.199
redness	19 (24.7)	18 (23.7)	1.000
swelling	19 (23.5)	14 (18.4)	0.563

Data are expressed as number (%) of patients, unless other wise indicated.
* Data of 7 cases are missing.

Discussion

- We found that the response rate of serotype 23F following simultaneous administration was not inferior to the response rate in sequential administration. In addition, multivariate analysis revealed no significant reductions in ORs for seroresponse rates in the simultaneous administration group in serotypes 23F, 3, 6B, and 19A.
- There were significant reductions in ORs for the seroresponse rates in the simultaneous administration group in serotypes 4 and 14. However, the clinical impact is expected to be low because the detection of serotypes 4 and 14 has decreased in invasive pneumococcal diseases and pneumonia worldwide[1,2,3].
- In the H1N1, H3N2, and B Phuket strains of influenza, there were no significant differences in ORs for seroprotection rates between the two groups.
- There were no significant differences in adverse events between the two groups.

Conclusion

- Simultaneous administration of 23-valent pneumococcal vaccine and quadrivalent influenza vaccine showed an acceptable immunoresponse compared to sequential administration of the two vaccines without an increase in adverse events.
- Simultaneous administration of the two vaccines may be a good strategy for improving the immunization rate.

References

✓1 Konosuke Morimoto, *et al*. PLoS One. 2015;10:e0122247.
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✓3 Elizabeth Miller *et al*. Lancet Infect Dis. 2011 Oct;11(10):760-768.

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