

Effects of the 23-Valent Pneumococcal Polysaccharide Vaccine on the Mortality of Pneumonia among Elderly over 70 Years Old after the Great East Japan Earthquake—PPV Vaccination Program in Iwate Prefecture, Japan

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Abstract

Objective: To estimate the efficacy of 23-valent pneumococcal polysaccharide vaccine (PPSV23) among the elderly, we analyzed the relationship between the mortality of the elderly for pneumonia and the vaccination rate of PPSV23 from 2008 to 2016 in Iwate Prefecture, Japan. **Study Design:** The present study was a retrospective, observational, database study adopting an ecological design. The mortality for pneumonia among the elderly over 70 years old from 2006 to 2016 in Iwate Prefecture was calculated based on the data from the Japanese Vital Statistics. We compared the mortality rate (MR) of pneumonia among the elderly over 70 years old between the low-vaccinated period (LVP) (2006-2010) and high-vaccinated period (HVP) (2012-2016) using a Poisson regression model. **Results:** While the vaccination rate of PPSV23 among the elderly over 65 years old was 3.3% in 2010, it increased rapidly up to 40.7% in 2012 and reached 66.4% in 2016. The MR ratio of the total population during HVP to the average MR during LVP was 0.749. The MR of the total population during HVP was significantly lower than that during LVP ($p < 0.001$). Notably, the MRs of both men and women during HVP were significantly lower than those during LVP ($p < 0.001$). The significant decrease in MR during HVP started in 2012 and continued up to 2016. **Conclusion:** The increase in vaccination rate of PPSV23 during HVP (2012-2016) may contribute to the decrease in mortality for pneumonia among the elderly over 70 years old in Iwate Prefecture.

Keywords

PPSV23, Mortality of the Elderly for Pneumonia

1. Introduction

Elderly people with pneumonia exhibit a high mortality rate worldwide. The elderly's high susceptibility to pneumonia is thought to be due to the senescence-related changes in the immune system and swallowing function [1] [2].

The percentage of the elderly over 65 years old exceeds 25% in Japan in 2015 [3]. Pneumonia is the third leading cause of mortality in Japan in 2017. *Streptococcus pneumoniae* is a major pathogen for both community-acquired pneumonia (CAP) and aspiration pneumonia, which influences morbidity and mortality in the elderly population [4] [5] [6].

For the treatment of pneumonia, especially with *Streptococcus pneumoniae*, new and effective antibiotics have been developed for several decades. They have been successful in reducing mortality associated with pneumococcal pneumonia, especially among children and young adults. However, despite the effectiveness of newly developed antibiotics for pneumonia in hospitalized patients, a concern has been raised that resistant strains have newly and repeatedly emerged [7].

Consequently, the need for preventive strategies against pneumonia with *Streptococcus pneumoniae* especially for young children, elderly and immune-compromised people has been stressed.

Currently, PPSV23 and the 13-valent pneumococcal conjugate vaccine (PCV13) are available for adults. The efficacy of the vaccine has been evidenced by large cohort trials, case-control studies on CAP, and meta-analyses concerning the protection from invasive *pneumococcal* disease [8]-[13].

Iwate Prefecture has a population of 1.23 million. The Great East Japan Earthquake occurred on March 11th 2011. Following the East Japan Great Earthquake Tsunami (GEJET), more than 5 thousand people in the Sanriku Sea Coast of Iwate Prefecture were forced to stay in evacuation centers for more than several months. Since the outbreaks of pneumonia among inmates of evacuation centers, an increase in mortality and hospitalization of the elderly due to pneumonia has been a concern in GEJET affected areas [14] [15] [16] [17]. As a consequence, PPSV23 was administered to the elderly over 70 years old in Iwate, Miyagi and Fukushima Prefecture; the PPSV23 was donated by the Japanese Red Cross Society in 2011 and 2012. Consequently, the percentage of the elderly over 65 years old who were administered PPSV23 increased rapidly from 3.3% in 2010 to 40.7% in 2012.

The aim of the current study is to evaluate the influence of increased PPSV23 vaccination on the mortality rate (MR) of pneumonia among the elderly over 70 years old in Iwate Prefecture. In the present study, we compared the MR of pneumonia between the low-vaccinated period (LVP) (2006-2010) and high-vaccinated

period (HVP) (2012-2016) in Iwate Prefecture, Japan.

2. Subjects and Methods

2.1. Study Design and Data Sources

The present study was a retrospective, observational, database study adopting an ecological design. The population of the elderly over 70 years old and the number of death caused by pneumonia in that population from 2006 to 2016 in Iwate Prefecture were calculated based on the data from the Japanese Vital Statistics in Iwate Prefecture (<http://www.pref.iwate.jp/hokenfukushi/toukei/054090.html>). The ratio of the vaccinated elderly over 65 years old in Iwate Prefecture was calculated based on the number of PPSV23 shipments in Iwate Prefecture.

2.2. Statistical Analysis

The vaccinated ratios of the elderly over 65 years old in 2009 and 2010 were 1.3% and 3.3%, respectively. Vaccination for the elderly over 70 years old was accelerated between October 2011 and March 2012. As a result, the vaccinated ratio of the elderly over 65 years old in 2012 increased rapidly to 40.7%. This rapid rise in vaccination rate was thought to be due to the vaccination of the elderly over 70 years old.

For a comparison of MR for pneumonia among elderly over 70 years old between the LVP and the HVP, the mortality rate ratio (MRR) was determined.

We defined LVP as 2006-2010 because the vaccination rate among the elderly over 65 years old was less than 3.3% during this period. HVP was defined as 2012-2016 because the vaccination rate increased rapidly up to 40.7% in 2012 and reached 66.4% in 2016. We excluded the data in 2011 because GEJET caused more than 7000 deaths due to drowning which was extraordinary.

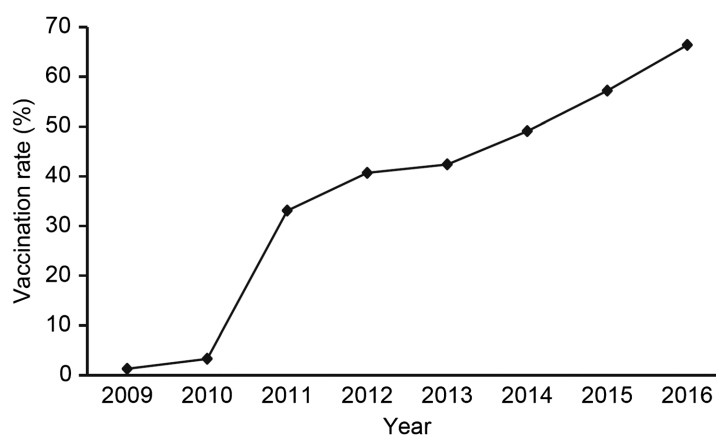
The MRR was computed for the HVP against the averaged MR of the LVP, using a Poisson regression model, controlling for age and sex.

All statistical tests were two-sided with a significance level of 0.05 and were carried out using IBM SPSS version 25 (IBM, Armonk, NY, USA).

3. Results

3.1. Changes in Vaccination Rate of PPSV23 among the Elderly over 65 Years Old in Iwate Prefecture

Since the vaccination rate of PPSV23 among the elderly over 65 years old remained 1.3% in 2009 and 3.3% in 2010, very few elderly people were vaccinated by PPSV23 before 2009 in Iwate Prefecture. After the Great East Japan Earthquake Disaster in 2011, a donation of PPSV23 vaccine by the Japanese Red Cross Society for the elderly over 70 years old led to a rapid increase in vaccination rate in the elderly in Iwate Prefecture. The vaccination rate increased rapidly up to 40.7% in 2012. Then, the vaccination rate of PPSV23 among the elderly over 65 years old continued to increase and reached 66.4% in 2016 (**Figure 1**).



Vaccination rate from 2006 to 2008 was lower than that of 2009.

Figure 1. Changes in vaccination rate of PPSV23 among the elderly over 65 years old in Iwate Prefecture.

Table 1. Adjusted MRs (95% CIs) and MRRs for death from pneumonia between LVP (2006-2010) and HVP (2012-2016).

	MR	95% confidence interval		MRR	95% confidence interval		P-value	P-value for interaction by sex
		lower	upper		lower	upper		
Total								
2006-2010	397	386	409	Reference				
2012-2016	298	289	307	0.749	0.724	0.775	<0.001	
Men								
2006-2010	635	612	658	Reference				
2012-2016	494	475	513	0.778	0.743	0.815	<0.001	0.248
Women								
2006-2010	225	214	237	Reference				
2012-2016	162	154	171	0.722	0.687	0.758	<0.001	

MR: mortality rate; MRR: mortality rate ratio; LVP: low vaccinated period; HVP: high vaccinated period Adjusted MR and MRR were adjusted for sex and age in total population and for age stratified by sex using the Poisson regression model.

3.2. Comparison of MR for Pneumonia among the Elderly over 70 Years Old between LVP and HVP

The MR for pneumonia during HVP was compared with LVP in **Table 1**. While the MR of the total population in LVP was 397, the MR during HVP decreased significantly to 298 ($p < 0.001$). The MRR of the total population during HVP against that during LVP was 0.749. Notably, the MRs of both men and women during HVP decreased significantly compared to those during LVP ($p < 0.001$, respectively).

3.3. Comparison of Averaged MR for Pneumonia during LVP with MR in Each Year during HVP among the Elderly over 70 Years Old

The MR of each year (2012, 2013, 2014, 2015, 2016) for pneumonia during HVP

was significantly lower than the average MR during LVP among the entire elderly population, and for both men and women over 70 years old in Iwate Prefecture (Table 2). As shown in Figure 2, MR started to decline significantly after 2012 and continued to decrease until 2016 ($p < 0.001$).

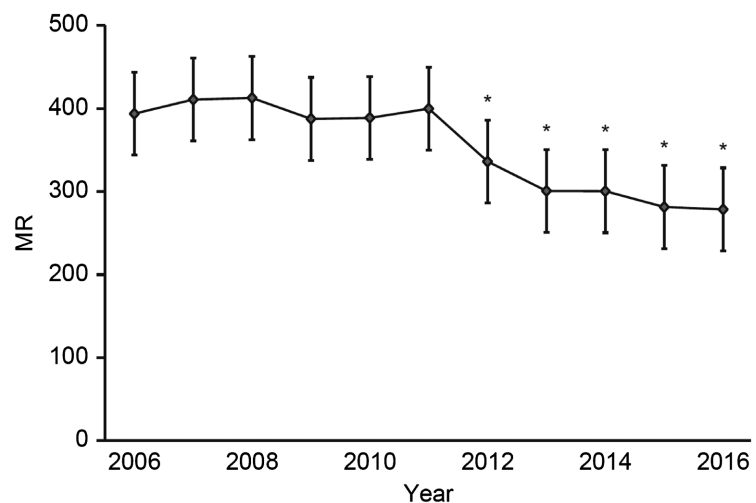
4. Discussion

We reported that MR for pneumonia among the elderly over 70 years old decreased significantly during HVP in Iwate Prefecture, Japan compared to that during LVP period (Table 1). In addition, the significant decrease in MR during

Table 2. Adjusted mortality rate ratios of pneumonia (95% confidence intervals) in HVP (2012-2016) compared with LVP (2006-2010) average.

Mortality rate ratio (vs. 2006-2010 average)		2012	2013	2014	2015	2016					
Total	MRR	0.84	0.75	0.75	0.71	0.70					
	95% CI	0.80	0.89	0.71	0.80	0.71	0.80	0.67	0.75	0.66	0.74
	P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Men	MRR	0.86	0.78	0.76	0.76	0.75					
	95% CI	0.79	0.93	0.72	0.84	0.70	0.82	0.70	0.82	0.69	0.81
	P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Women	MRR	0.83	0.73	0.75	0.66	0.65					
	95% CI	0.76	0.90	0.67	0.80	0.69	0.82	0.60	0.72	0.60	0.71
	P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

LVP: low vaccinated period; HVP: high vaccinated period.



The MR of each year during the HVP (2012-2016) was significantly lower than the average MR during the LPV. *: $p < 0.001$.

Figure 2. Changes in MR for pneumonia among the elderly over 70 years old in Iwate prefecture.

HVP started in 2012 as shown in **Table 2**. The rapid rise in vaccination rate from 3.3% in 2010 to 40.7% in 2012 might have caused the significant decrease in MR during HVP (**Table 1**).

Pneumonia is a major cause of mortality worldwide, and *Streptococcus pneumoniae* is an important pathogen for CAP in both children and the elderly [18]. Approximately, 1.6 million deaths occur annually due to pneumococcal diseases worldwide, with the highest incidence rate in children under 2 years and adults over 65 years of age [19] [20] [21]. CAP is also a major cause of adult mortality in Asia (22). Treatment of pneumonia including antibiotics and hospitalization has been an increasing economic burden [22]. A prompt therapy with antibiotics is recommended for *pneumococcal pneumonia*. However, increasing drug-resistant strains and the lack of development of new antibiotics are main concerns in the battle against these bacterial infections [23] [24].

The strategy of preventing pneumonia with an effective vaccine for *Streptococcus pneumoniae* has been studied for several decades. As a consequence, effective pneumococcal polysaccharide conjugate vaccines against pneumococcal disease such as PPSV23 and PVC13 became available. Bonten *et al.* evaluated the efficacy of PCV13 for the prevention of vaccine-type invasive and noninvasive community-acquired pneumonia in adults 65 years of age or older [25].

Concerning the effectiveness of PPSV23 in general population and the elderly, Tsai *et al.* reported that PPSV23 showed significantly lower odds ratios (ORs) for pneumonia hospitalization and death from pneumonia in comparison between the vaccinated and non-vaccinated elderly people over 75 years old in a nation-wide study (n = 1,078,955) in Taiwan region [26]. Maruyama *et al.* demonstrated that pneumococcal pneumonia was significantly more frequent in the placebo group than in the vaccine group and that death from pneumococcal pneumonia was significantly higher in the placebo group than in the vaccine group among 1006 nursing home residents in Japan by their perspective, randomized, placebo controlled double-blind study [5]. Leventer-Roberts *et al.* reported that the PPSV23 vaccine was effective against the most severe invasive forms of pneumococcal disease among 470,070 individuals aged 65 years or older in their retrospective case-control study [27]. Consistently, we revealed the significant decrease in MR for pneumonia among approximately 250,000 elderly population over 70 years old in Iwate Prefecture during the HVP (2012-2016) compared to that during the LVP (2006-2010). Ochoa-Gondar O *et al.* demonstrated the protective effect of PPSV23 against both pneumococcal and all-cause CAP in the population-based cohort study involving 27,204 individuals aged 60 years or older in Spain [28]. Taken together, the decrease in MR for pneumonia during HVP in our study might be due to the protective effect against both pneumococcal and all-cause CAP.

PPSV23 has been available for adults since 2006 as an anti-pneumococcal vaccine in Japan. However, the vaccination rate of PPSV23 remained low until 2010, although it was generally recommended to those at high risk of pneumococcal

pneumonia [29]. In 2011 and 2012, PPSV23 was administered free of charge as a medical support to the elderly over 70 years old in GAJET affected areas including Iwate Prefecture. This medical support accelerated the increase in vaccination rate of PPSV23 from 3.3% in 2010 to 40.7% in 2012. We determined the vaccination rate of PPSV23 among the elderly over 65 years old. On the other hand, the rapid rise in vaccination rate in 2012 was due to the increase of vaccination rate among the elderly over 70 years old. Therefore, we analyzed MRs of the elderly over 70 years old during LVP and HVP.

The outbreaks of pneumonia among the elderly in evacuation centers after GEJET were reported [17]. The increase in mortality and hospitalization of the elderly due to pneumonia was a serious problem in GEJET affected areas. Under these circumstances, a donation of PPSV23 to the elderly over 70 years old in GEJET affected area including Iwate Prefecture, was proposed by the Japanese Red Cross Society. PPSV23 was administered to the elderly over 70 years old from October 2011 to March 2012 in Iwate Prefecture. While the vaccination rate of PPSV23 among the elderly over 65 years old was 3.3% in 2010, it increased rapidly up to 40.7% in 2012 and reached 66.4% in 2016. As shown in **Table 1**, the MR of pneumonia during HVP (2011-2016) among the total population over 70 years old was significantly lower than that during LVP (2006-2010). Concerning the gender difference, the population of women over 70 years old was about 150,000, which was 1.5-fold bigger than that of men in Iwate Prefecture, Japan. The MRs for pneumonia in women over 70 years old was significantly lower than those of men from 2006 to 2016. Notably, the MRs of both men and women over 70 years old during HVP were significantly lower than those during LVP. In addition, the statistical significance for interaction by sex was not observed as shown in **Table 1**. In addition, there is no big change in the percentage of population by age in Iwate Prefecture (<https://www.population-map.com/iwate#age>). In Japan, public subsidies for PCV7 for children under 5 years old started in 2010. The prevalence of invasive forms of pneumococcal disease in children after public subsidies for PCV7 was compared to 2010, it decreased by 57% by 2013 [30]. It is possible that changes in pediatric prevalence affected mortality in the elderly. On the other hand, Aomori Prefecture, which is adjacent to Iwate Prefecture, suffered only minor damage from the GEJET, so no vaccines were donated by the Japanese Red Cross Society. There was no significant difference in mortality before and after the GEJET (**Figure S1**). It is unlikely that there is a large difference in pediatric pneumococcal vaccination rates between Iwate and Aomori prefectures. The difference in changes in MR of pneumonia in the elderly aged 70 years and over in Iwate Prefecture and Aomori Prefecture is thought to be due to the difference in changes in pneumococcal vaccination rates.

In conclusion, the present study suggested that the increase in vaccination rate of PPSV23 might be associated with the decrease in MR for pneumonia among the elderly over 70 years old in Iwate Prefecture, Japan.

Author Contributions

KY and HN conceptualized and designed the study. KT contributed to the statistical analysis of the data. KS, YU and MA contributed to the interpretation of data.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

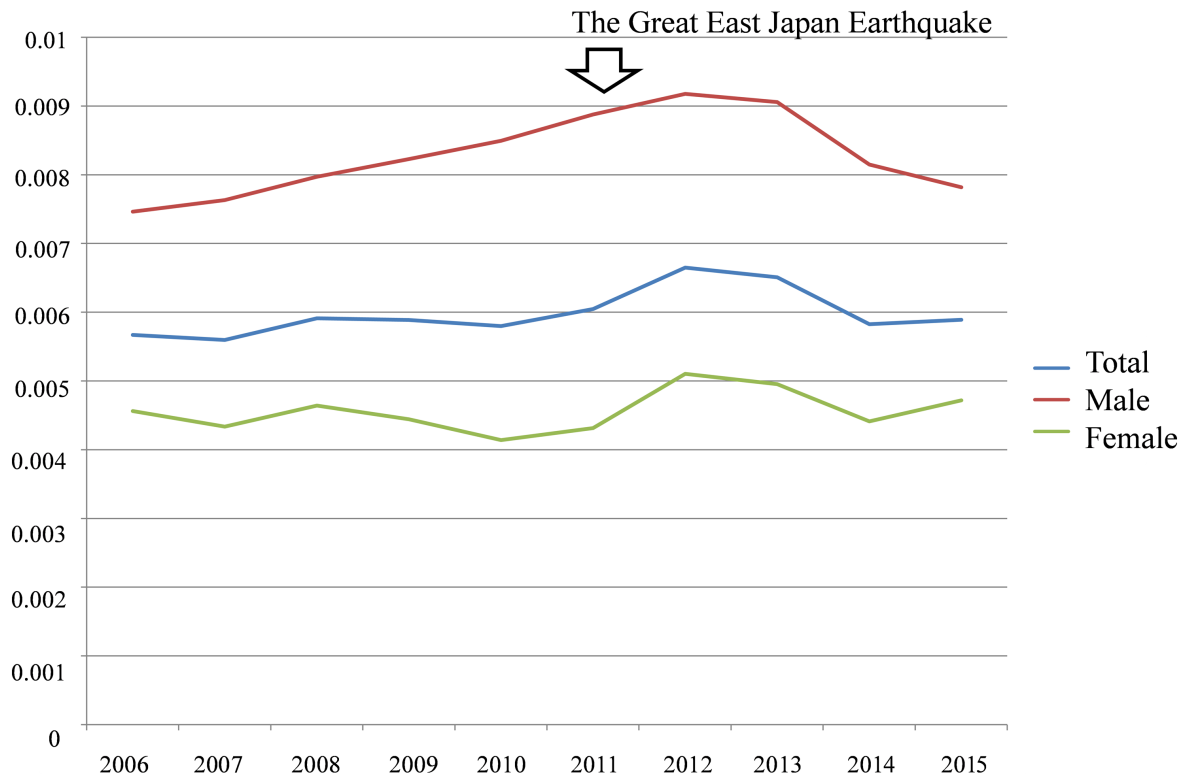
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Supplement



There was no significant difference in mortality before and after the GEJET.

Figure S1. Elderly pneumonia mortality rate in Aomori Prefecture.