4. Discussion

In this population-based prospective cohort study among community-dwelling elderly in Japan, influenza vaccination reduced the risk of ILI with fever more than 38 °C. The protective effect was greater among low-risk group than among high-risk group. The study of influenza vaccine effectiveness in persons aged 65 years and over living in the community was limited [12–15], especially the effectiveness for ILI [20,21]. Vu et al. performed a meta-analysis for ILI, and estimated 35% as the reduction, which was similar to the estimates in the study of healthy adults [21]. A placebo-controlled trial from the Netherlands confirmed that vaccination reduced the risk of clinical and serologic influenza among the elderly by 58%, however, vaccine effectiveness was less pronounced for self-reported influenza [20,21]. In that study, all participants were sent questionnaires regarding possible influenza episodes and symptoms twice, namely at 10 and 23 weeks after vaccination. Since it was a retrospective investigation, some information bias might have influenced the results. Accuracy of self-information is critical to evaluate the vaccine effectiveness for ILI, and a complete follow-up and an adequate case definition is essential.

The advantage of our study is that we observed each individual study subject prospectively with an equal intensity throughout the epidemic period. To measure the outcome, we asked the study subjects to note their body temperature and symptoms on the provided record sheet (symptoms diary) when they had fever (≧37.0 °C) and we interviewed them for ILI by telephone at least once a month. Therefore, we could confirm ILI, as well hospitalization and death. In addition, this prospective design could minimize selection bias and recall bias, in comparison to a retrospective design. One population-based follow-up study with a telephone among elderly citizens in Taiwan reported the vaccine effectiveness for reducing hospitalization and death, however, it could not evaluate the vaccine effectiveness for ILI, due to a large number of lost subjects during the follow-up (13.8%) [15]. If the untraceable subjects included many ILI and serious influenza cases, then the results would be negatively affected. Devising the criteria for the study participation enabled us to achieve an excellent follow-up rate (98.7%).

Observational cohort studies among community-dwelling elderly mostly address the benefits of influenza vaccination for hospitalization and death [2–11]. Although several studies have demonstrated the vaccine effectiveness for clinically diagnosed influenza, such reductions were inconsistent, ranging 15–50 % [10,23]. Vaccinations tended to reduce the number of clinically diagnosed influenza cases in the present study, however, protective effect was not statistically significant and it also differed based on the risk conditions. Because the seriousness of influenzal symptoms and hospital visits are not necessarily related in Japan, a misclassification of clinical diagnosed influenza may occur due to the fact that not every influenza patient visits a hospital. In comparison to the low-risk group, the high-risk group tended to visit the hospital more frequently and was also more likely to be diagnosed to have influenza, so that a reduction of clinical influenza might thus be observed.

Our results indicated that self-reported ILI may thus be a suitable method for showing the protective effect of vaccination among community-dwelling elderly individuals, as long as they are reported completely, because they are not affected by hospital visits. In general, non-differential misclassification, which means that ILI including non-influenzal disease and non-ILI including influenza, results in an underestimation of vaccine effectiveness. We observed that the ORs decreased as the fever threshold increased. When fever was equal to and higher than 38.5 °C, the OR was almost 0.4. Two possibilities to explain this may thus be proposed. First, the misclassification of "non-influenza" was avoided by setting a clear limit for fever (namely, equal to or higher than 38.5 °C) thereby allowing us to better identify the true effect of influenza vaccination. Second, vaccination may also prevent higher fever itself.

This study provided an additional possibility that the target outcome of vaccination differed according to the subjects' medical conditions, even among community-dwelling elderly. The protective effect for ILI was greater among the low-risk group, on the other hand, that for influenza hospitalization was only seen among the high-risk group. Several studies investigated the vaccine effectiveness according to the risk-conditions [3,5,7,9–11], however, the results are inconsistent. A previous cohort study using a computerized database in the Netherlands investigated the effectiveness of an influenza vaccine according to the risk conditions in the community and also reported mortality to be significantly reduced in elderly with comorbidity (OR, 0.67; 95% CI, 0.48–0.94), although vaccination failed to show any protective effect for pneumonia [10]. Whereas the sample size of our study was sufficient to evaluate the effect for ILI by means of a telephone follow-up, it was not large enough to detect any statistically significant effect for mortality and hospitalization. However, our findings suggest that vaccination to elderly in community is beneficial for both high-risk and low-risk groups.

In the absence of randomization, potential problems of this study might be related information bias and confounding by indications. Information bias for vaccination was unlikely, since we verified all self-reported information with the records of the city vaccination program. The information biases for self-reported symptoms were minimized, due to prospective, frequent and complete follow-up. On the other hand, some confounding factors regarding the indications were likely associated because some chronic diseases, as well as a history of hospitalization might be independent risk factors for an increased risk of influenzal disease, as was a history of influenza vaccination. Even when these factors were adjusted by a multivariate analysis, no all residual confounding factors could be excluded. However, such confounding factors may have resulted in an underestimation of vaccine effectiveness. Hence, our estimates are conserva-

tive, and the real effects may actually be higher than herein reported.

In conclusion, our results indicated that, influenza vaccination was thus found to be associated with a decreased ILI during the epidemic period in community-dwelling elderly. The above risk reduction was greater under low-risk conditions than that under high-risk conditions. The results were inconclusive for preventing hospitalization and death, due to an inadequate sample size. However, our findings support the finding that all elderly individuals substantially benefit from vaccination even in a season of mild influenza activity and also when the antigenic match between the vaccine strains and the circulating strains are not closely matched.

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