

## 博士論文の要旨及び審査結果の要旨

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学位授与の要件	学位規則第4条第1項該当
博士論文名	Effectiveness of the quadrivalent inactivated influenza vaccine in Japan during the 2015-2016 season: A test-negative case-control study comparing the results by real time PCR, virus isolation (2015年～2016年のインフルエンザシーズン中の日本における4価不活化インフルエンザワクチンの有効性:リアルタイムPCR)
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### 博士論文の要旨

Background: We estimated influenza vaccine effectiveness (VE) in 2015-2016 season against medically attended, laboratory-confirmed influenza, using test-negative case-control design. Quadrivalent inactivated vaccine (IIV4) with following components A/California/7/2009 for A(H1N1)pdm09, A/Switzerland/9715293/2013 for A(H3N2), B/Phuket/3073/2013 for B/Yamagata lineage and B/Texas/2/2013 for B/Victoria lineage was first introduced in Japan. Following dosage of vaccine is recommended in Japan: for children 6 months to 2 years of age two 0.25 ml doses of vaccine 2 to 4 weeks apart, for children 3-12 years two 0.50 ml doses of vaccine 2 to 4 weeks apart, for children over 13 years of age and over only one 0.5 ml dose. During the study period in Japan influenza A(H1N1)pdm09 cocirculated with B/Yamagata and B/Victoria.

Method: We based our case definition on two laboratory tests, real-time reverse transcription polymerase chain reaction (RT-PCR), and virus isolation and compared VEs based on these tests. In addition, VE was evaluated by rapid diagnostic test (RDT), which is common in clinical practice in Japan. Nasopharyngeal swabs were collected from outpatients who visited clinics with influenza-like illness (ILIs) in Hokkaido, Niigata, Gunma and Nagasaki prefectures. One vaccine dose was considered as vaccinated for any age of patients. Underlying conditions were not included in this analysis due to mainly healthy children were enrolled. Sequencing of the HA genes of influenza A(H1N1)pdm09, B/Yamagata and B/Victoria were run, the phylogenetic tree analysis was constructed.

Results: Among 713 children and adults enrolled in this study, 578 were influenza positive by RT-PCR including, 392 influenza A and 186 influenza B, while 135 were tested negative controls.

The adjusted VE by RT PCR for all ages against any influenza was low protection of 36.0% (95% confidence interval [CI], 3.1% to 58.6%), for influenza A was 30.0% (95% CI: -10.0% to 55.5%), and influenza B was moderate 50.2% (95% CI: 13.3% to 71.4%). Adjusted VE for virus isolation for A(H1N1)pdm09 was 37.1% (95% CI: 1.7% to 59.7%), Yamagata lineage 51.3% (95% CI: 6.4% to 74.7%) and Victoria lineage 21.3% (95% CI: -50.0% to 58.9%). VE was highest and protective in 0-5 years old group against any influenza and influenza A and B/ Yamagata, but the protective effect was not observed for other age groups and B/Victoria. RDT demonstrated concordant results with RT PCR and virus isolation. Sequencing of hemagglutinin gene showed that all A(H1N1)pdm09 belong to clade 6B including 31 strains (88.6%), which belong to clade 6B.1 possessing S162N mutations, which is located in antigenic site Sa and may alter antigenicity and affect VE for A(H1N1)pdm09.

Conclusions: IIV4 influenza vaccine during 2015-2016 was effective against A(H1N1)pdm09 and the two lineages of type B. Younger children was more protected than older children and adults by vaccination.

#### 審査結果の要旨

Background: The efficacy (VE) of the tetravalent inactivated vaccine (IIV4) introduced in 2015 was estimated in influenza patients during the 2015-2016 season.

METHODS: Applicants compared VEs based on virological results. Influenza samples were collected from outpatients who were diagnosed with influenza-like diseases in Hokkaido, Niigata, Gunma and Nagasaki prefectures.

RESULTS: Adjusted VE for all ages was 36.0% (95% CI 3.1%-58.6%). The VE for influenza A was 30.0% (95% CI: 10.0%-55.5%), and the B type was 50.2% (95% CI: 13.3%-71.4%). Adjusted VE of A(H1N1)pdm09 is 37.1% (95%CI: 1.7%-59.7%), Yamagata system is 51.3% (95%CI: 6.4%-74.7%) and Victoria system is 21.3% (95%CI). : -50.0%-58.9%). VE was observed in A and B type Yamagata strains at ages 0-5. In other age groups, no VE was found for all influenza types, and no VE for Victoria type B strains was found in all age groups.

Discussion: The reason for the low VE against A(H1N1)pdm09 may be the difference in antigenicity between the vaccine strain and the epidemic strain.

CONCLUSION: The 2015-2016 IIV4 influenza vaccine was effective against A(H1N1)pdm09 and B.