

# Seasonal influenza and vaccine herd effect

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The seasonal influenza vaccine programs in many regions aimed to protect most vulnerable population, but current trivalent influenza vaccine does not provide sufficient effectiveness among people under high risk for severe outcome of the influenza. The vaccine herd effect (VHE) is the extra protection of non-immune high risk persons, with increase of immunity among vaccinated healthier persons which prevents circulation of influenza in the community. Accumulating evidences are supporting the immunization of extended population with regard to the VHE.

**Keywords:** Vaccine herd effect, Vaccine herd immunity, Influenza vaccine

## Introduction

The direct efficacy and effectiveness of the inactivated influenza vaccination among healthy is relatively well-known. The (direct) vaccine efficacy (VE) is expressed as a proportionate reduction in influenza attack rate between the unvaccinated and vaccinated groups [1,2] and is also equal to (1-Relative Risk). VE is calculated using accurate biological diagnosis outcomes which could usually be given after a prospective randomized interventional study. However, the (direct) vaccine effectiveness is more likely a field efficacy of the vaccine looking for various outcomes of vaccine seen in non-interventional setting (Table 1). A randomized double blinded study among healthy healthcare professional (n=361 person-winters) resulted the laboratory confirmed influenza was 87.3% reduced and absenteeism was 53.1% reduced in vaccine group [3]. Although febrile respiratory illness was not significantly different between two groups, this study supports the healthcare worker vaccination to prevent influenza circulation among hospitalized patients. A case control study showed seasonal influenza vaccine prevented 32-39% hospital admission with pneumonia and influenza and 43-65% related hospital death among community participants of age  $\geq 45$  [4]. The limitations of this study exist not only in the design but also in the diagnosis according to the ICD-9 hospital discharge record instead of an accurate laboratory diagnosis. The vaccine herd effect (VHE) is a VE among unvaccinated contacts (Table 1). In this review current updates on influenza vaccine studies which support the immunization of extended population with regard to the VHE will be discussed.

**Table 1.** Definitions of vaccine efficacy, effectiveness and herd effect [2]

Vaccine efficacy	$\frac{(AR[U] - AR[V]) \times 100}{AR(u)} = (1 - RR) \times 100$
Vaccine effectiveness	$\frac{(Odds[U] - Odds[V]) \times 100}{Odds(u)} = (1 - OR) \times 100$
Vaccine herd effect	Vaccine efficacy among unvaccinated contacts

AR, attack rate; U, unvaccinated; V, vaccinated; RR, risk ratio; OR, odds ratio.

### Failure to Protect Elderly and Chronically Ill Persons

Since the introduction of influenza vaccination after the World War II, immunization against seasonal influenza was focused on reducing mortality and morbidity of elderly, chronically ill persons, pregnant women and young children [5]. This old policy especially dates back to the 1957 and 1968 influenza pandemic which caused significant mortality among these populations. The annual mortality associated with the seasonal influenza ranged now from 250,000 to 500,000 in the world and 3,349 to 48,614 [6] in the United States alone [7].

However, the concerns over the weakness of inactivated influenza vaccine to protect the elderly had been raised since 1960's [8]. Despite relative success on reducing laboratory-confirmed influenza virus infection by VE 66% among healthy children [9,10], VE was especially diminished in the nursing home residents due to age related immunosenescence and comorbidities [11]. Moreover, vaccinating selected population unlikely to reduce the entire burden of seasonal influenza since the majority of infection circulates among younger age group [12,13]. Consequently, from 1972 through 1992 seasonal influenza vaccination program to protect high risk group was not successful in reducing mortality [14]. Although considerably more influenza vaccines were used during 1990 to 2000 seasons compared to previous decades, the related deaths were increased in the United States [15]. A systematic review on effectiveness of seasonal influenza vaccine among elderly demonstrates only limited benefit [16]; in long-term care facility, the trivalent inactivated vaccine's effectiveness against influenza like illness was 23% (95% confidence interval [CI], 6 to 36), against pneumonia was 46% (95% CI, 30 to 58) and against influenza or pneumonia death was 42% (95% CI, 17 to 59). However the benefits are not significant among community participants.

### Lack of Evidence to Support Risk for Severe or Complicated Influenza

Elderly, pregnancy, comorbidities were known to be associated with increased risk for severe outcomes of the influenza. The influenza vaccination before 2009 had strong emphasis on protecting these populations. However most evidences were based on ecological studies [17,18], on studies with insufficient sample size or studies missing adjustment for risk assessment. A recent systematic review which included studies during the last 2009 pandemic concluded that the level of evidence to support risk for severe influenza was low and well accepted risk factors like pregnancy and ethnicity were even not confirmed as risks [19].

### The Indirect Effect: VHE of Seasonal Influenza Vaccination

With the impact of the school closure on diminishing peak wave in 1957-1958 pandemic, school had been suggested for an ideal place for vaccination [20]. The very first intervention to vaccinate healthy young school children was the "Tecumseh study" in 1969 [21]. Monovalent influenza vaccine A (H3N2) was given to school children of the entire study city, with an uptake rate of 86% and compared outcomes among entire age group with the control city without such program. The outcomes were measured by the geometric mean of antibody titer which was 61 hemagglutinins units of A<sub>2</sub>/Aichi/2/68 and by acute respiratory illness which was reduced in 1/3 with vaccination. The observation was specifically linked to the influenza A only, there was no difference of influenza B between groups. This Tecumseh study suggested the indirect herd benefit of childhood vaccination among entire age group, but accurate laboratory confirmation of the influenza was lacking.

Japan had school influenza vaccination program since 1962 but it was abandoned after 1987, and winter pneumonia and influenza mortality had been increased after that period in comparison with the United States [22]. This observation indirectly suggests the potential role of school vaccination in reducing mortality from influenza among older persons [20].

A systematic review on universal childhood influenza vaccination suggested VE in non-vaccinated contacts (family members) ranged from 24% to 30% (Table 2) [23-25]. The VHE as an indirect effect of vaccination is calculated as same manner as the VE but outcome compared between unvacci-

**Table 2.** Study details of vaccine trials showing herd efficacy (efficacy in non-vaccinated contacts) of influenza vaccination

	Monto et al. (1970) [21]	Esposito et al. (2003) [24]	Principi et al. (2003) [25]	Loeb et al. (2010) [26]
Design	Nonrandomized intervention study	Cluster randomized control study	Cluster randomized control study	Cluster randomized control study
Patients	School children (n=3,159)	Children with recurrent respiratory infections (n=127)	Children with recurrent respiratory infections (n=303)	Children and adolescents (n=947) in Hutterite community
Intervention (study vaccine)	Vaccine in study city Monovalent inactivated influenza A (H3N2) vaccine	Vaccine in study children Trivalent inactivated influenza vaccine, intranasal	Vaccine in study children Trivalent inactivated influenza vaccine, intramuscular	Vaccine in study children and adolescents Trivalent inactivated influenza vaccine, intramuscular
Comparators	No vaccine in control city	Placebo vaccine in control children	Placebo vaccine in control children	Control (hepatitis) vaccine in study children and adolescents
Outcomes measured	Respiratory tract infection	Respiratory tract infection	Respiratory tract infection	Laboratory confirmed influenza (PCR)
Conclusion (herd efficacy)	Decrease of influenza A in entire age group	Vaccine efficacy in contacts (24%; p=0.0001)	Vaccine efficacy in contacts (30%; p=0.0005)	Vaccine efficacy in contacts (61%; p=0.03)

PCR, polymerase chain reaction.

nated contacts of vaccine and control cohorts (Table 1). A recent cluster randomized controlled trial in Hutterites colonies in Canada estimated more accurately the herd effect of the trivalent influenza vaccine [26]; colonies were randomized to vaccinated children and adolescents with either study influenza vaccine or control vaccine, and polymerase chain reaction based laboratory confirmed influenza were compared between non-vaccinated older population of both groups. The protective effectiveness in non-vaccinated adults of study colonies was 61% (95% CI, 0.08 to 0.83; p=0.03) for reducing laboratory-confirmed influenza. Number needed to treat was 25.0 persons.

### Extending Benefit of VHE in Seasonal Influenza

A trivalent live attenuated influenza vaccine (LAIV) given to school children was associated with greater direct efficacy as well as herd protection among community adult residents [27]. The efficacy and the safety compared to inactivated trivalent influenza vaccine was not significantly different [28]. The theoretical advantage of LAIV rely on the fact that the viruses in LAIV replicate on epithelial cells to induce immunity including local mucosal IgA antibody [29]. Extending LAIV coverage could potentially results better herd efficacy, given its higher efficacy among younger populations.

Traditionally seasonal influenza vaccination program, including school vaccination was considered as an important component of pandemic preparedness [20], but whether trivalent seasonal influenza vaccination program alone is syn-

ergistic in preventing the pandemic strain or not is yet unclear. During the 2009 H1N1 pandemic, the outbreak of H1N1 was unexpectedly associated with receipt of trivalent seasonal influenza vaccination [30]. One of the potential explanations for this observation is “heterosubtypic immunity” among influenza subtypes [31]. However, current policy regarding seasonal influenza vaccination should not be discouraged because of its independent value on preventing mortality related with seasonal influenza. Therefore, the development of additional monovalent pandemic vaccine should be implemented in case of new pandemic [32].

### Conclusion

Current influenza vaccine program focused on high risked population does not provide sufficient effectiveness on preventing severe outcome of the influenza. Implementing the herd effect of the seasonal influenza vaccination, universal immunization will potentially further protect vulnerable population under risk of influenza. The evidences supporting such VHE are increasing in the quantity and the quality; vaccine studies now use laboratory-confirmed diagnosis with large number of participants.

However, with the limitation of vaccine supply, influenza vaccination was long recommended to the selected prioritized group of population under risk of severe complication. Current global vaccine production capacity is yet far from able to meet the basic needs for pandemic vaccine but production capacity is recently extended to broader World Health Organization region [33] including the Republic of Korea since

2008 [34]. As the universal vaccination program of healthy population requires significantly increased global production of the vaccine, increased benefit with mass vaccination with current trivalent influenza vaccine is expected by the time the vaccine supply meets global needs.

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