

REVIEW



## Effects of influenza immunization on pneumonia in the elderly

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### ABSTRACT

Influenza virus is a common pathogen implicated in respiratory tract infections, annually affecting up to 20% of the general population, and pneumonia is a leading cause of death after influenza infection. Post-influenza pneumonia is especially common in the elderly and chronically ill patients. The risk of post-influenza pneumonia is significantly increased according to the number of concurrent comorbidities. Vaccination is the primary measure used to abate influenza epidemics and associated complications. In meta-analyses, influenza vaccine significantly reduces pneumonia- and influenza-related hospitalizations, with a vaccine effectiveness of 25–53%. However, considering the poor effectiveness of conventional influenza vaccines in the elderly, several highly immunogenic influenza vaccines have been developed. Further evaluations of the comparative effectiveness of diverse vaccine formulations are warranted to assess their utility for preventing influenza infection, post-influenza pneumonia, and related hospitalization/mortality. Based on cost-effectiveness and budget impact analysis, influenza vaccination strategies should be tailored in the elderly.

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### Introduction

Influenza virus is a common pathogen implicated in respiratory tract infections, annually affecting up to 20% of the general population, and pneumonia is a leading cause of death after influenza infection.<sup>1,2</sup> The incidence (0.1 – ≥10%) and case-fatality (<0.1 – 60%) of influenza pneumonia vary depending on antigenic variation and the virulence of circulating viruses.<sup>3</sup> Seasonal influenza viruses cause 200,000–400,000 deaths per year during annual epidemics, while the 1918 H1N1 Spanish pandemic influenza virus was responsible for >40 million deaths.<sup>1,4,5</sup>

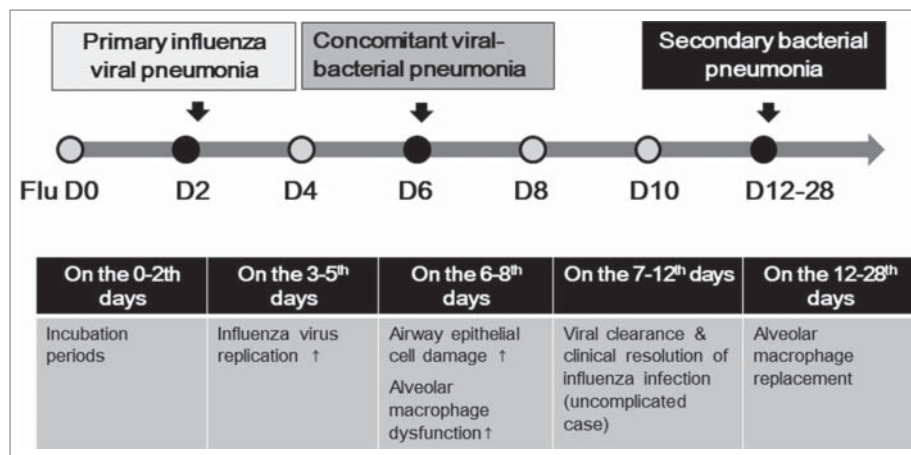
There are three types of influenza-related pneumonia, although clear distinctions may not be feasible: primary viral pneumonia, concomitant viral-bacterial pneumonia and secondary bacterial pneumonia (Fig. 1). Primary viral pneumonia is the least common type of influenza-related pneumonia, although it is more common in cases of avian influenza pneumonia (H5N1 and H7N9 viruses).<sup>6</sup> Primary viral pneumonia can progress rapidly to severe pneumonia within 24 hours, and has a high case-fatality rate of 10–60%.<sup>6,7</sup> Concomitant viral-bacterial pneumonia is at least three times more common than primary viral pneumonia, and this type of pneumonia tends to develop approximately 6 days following influenza infection.<sup>6,8,9</sup> Among bacterial co-pathogens, *Streptococcus pneumoniae* and *Staphylococcus aureus* are the most common, followed by *Klebsiella pneumoniae* and *Haemophilus influenzae*.<sup>8</sup> The case-fatality rate of concomitant viral-bacterial pneumonia is

reported to be about 10%.<sup>6</sup> It can be difficult to clinically distinguish concomitant viral-bacterial pneumonia from primary viral pneumonia, but it is important to administer antibiotic agents against bacterial co-infection at optimal times in terms of clinical outcomes. Although levels of C-reactive protein and procalcitonin are useful for differential diagnosis accompanying bacterial infections, current influenza guidelines recommend that clinicians should treat all influenza-related pneumonia cases with antibiotics.<sup>10,11</sup> Secondary bacterial pneumonia usually develops 1–2 weeks after influenza-like illness following a brief period of improvement. Patients with secondary bacterial pneumonia show typical symptoms and signs of bacterial pneumonia (fever, chill, cough, purulent sputum, dyspnea) with a case fatality rate of about 7%.<sup>6</sup>

Pneumonia is the leading cause of influenza-related morbidity and mortality during both pandemic and seasonal epidemic periods. Although influenza vaccine is effective for preventing respiratory illness and reducing influenza-related hospitalization, it remains unclear whether influenza vaccine can decrease the risk of influenza-related pneumonia. This review focuses on the pathogenesis of influenza pneumonia and the effectiveness of influenza vaccine against pneumonia.

### Pathogenesis of influenza-related pneumonia

Influenza viral proteins and host immune responses both play pivotal roles in the development of pneumonia. Influenza virus



**Figure 1.** Schematic description of pathophysiological changes and development of pneumonia after influenza infection.

is composed of eight RNA gene segments, encoding hemagglutinin (HA), neuraminidase (NA), nucleoprotein (NP), M1, M2, nonstructural (NS) 1 protein, NS2 protein, polymerase acidic (PA) protein, polymerase basic (PB) 1 protein, PB1-F2 and PB2 protein. Among these proteins, influenza virus NS1 antagonizes type I IFN expression from infected cells during early stages. Type I IFNs play an important role inducing innate resistance to influenza viral infection.<sup>2</sup> HA is associated with tropism for the target cells in the respiratory tract. Seasonal influenza viruses usually bind to  $\alpha$ 2,6 sialic acid residues on the epithelial cells of the upper respiratory tract in humans, whereas avian influenza viruses (A/H5N1 and A/H7N9) preferentially bind to  $\alpha$ 2,3 sialic acid residues of the lower respiratory tract, thereby infecting type 2 pneumocytes.<sup>12</sup> Thus, avian influenza viruses can cause severe primary viral pneumonia with limited transmission. In comparison, seasonal influenza viruses can spread widely, but severe viral pneumonia is rare. Of note, the 2009 pandemic influenza A/H1N1 virus had a D222G mutation, which increased its affinity to  $\alpha$ 2,3 sialic acid receptors, and was thereby more likely to cause pneumonia.<sup>12</sup> On the other hand, PB1-F2 is a well-known virulence factor that can cause apoptosis and cytokine storm.<sup>2,8</sup> Mutations on PB1-F2 encoding genes might affect virulence. The N66S substitution in PB1-F2 increased virulence in the 1918 Spanish pandemic influenza A/H1N1 and H5N1 influenza viruses, while PB1-F2 truncation in the 2009 pandemic influenza A/H1N1 virus might be associated with the low case-fatality rate observed that year.<sup>2,8,10,12</sup>

In addition to causing primary viral pneumonia, influenza viruses contribute to the development of bacterial coinfections due to enhanced bacterial adherence in the respiratory tract and paradoxical suppression of the host immune system. There are several mechanisms by which bacterial adherence may increase.<sup>2,6,8,9</sup> First, influenza virus may induce epithelial cell death, exposing the basal cell layer and basement membrane, which in turn increases bacterial binding to fibronectin and glycoproteins of basal progenitor cells.<sup>2,13</sup> Second, influenza virus also up-regulates bacterial receptors including polymeric immunoglobulin receptor (pIgR) and platelet-activating factor receptor (PAFR).<sup>2,8,9</sup> Third, influenza viral NA cleaves respiratory epithelial cell sialic acids, leading to increased expressions

of bacterial binding receptors.<sup>2,8,9</sup> With respect to paradoxical immune suppression, alveolar macrophage function is impaired by dysregulated cytokine responses after influenza infection.<sup>2,9</sup> Alveolar macrophage dysfunction is associated with IFN- $\gamma$ -mediated downregulation of the scavenger receptor MARCO, reduced production of TNF- $\alpha$  by natural killer (NK) cells, activation of transforming growth factor (TGF)- $\beta$  by NA and disproportionate release of immunosuppressive cytokine (IL-10) from respiratory epithelial cells.<sup>2,9</sup> Type I IFN also paradoxically suppresses alveolar macrophages.<sup>2</sup> As a consequence, impaired alveolar macrophages release diminished amounts of neutrophil-activating chemokines such as macrophage inflammatory protein 2 (MIP-2) and keratinocyte-derived chemokine (KC).<sup>2</sup> Besides impaired recruitment in alveolar spaces, influenza-affected neutrophils have functional defects in phagocytic activity, myeloperoxidase production, respiratory burst, and lysozyme secretion.<sup>2</sup> Airway tissue damage is most severe around 6 days after influenza infection, and alveolar macrophage dysfunction is greatest 7–8 days post-infection (Fig. 1).<sup>2,6,8,9</sup> The altered alveolar macrophages are then replaced over the next two weeks.<sup>8</sup> Thus, patients with influenza are most susceptible to bacterial co-infection 6–8 days after infection, and remain at high risk for secondary bacterial pneumonia up to 3–4 weeks post-infection.<sup>2,6,8,9</sup>

### **Increased risk of pneumonia development after influenza infection in chronically ill patients**

Elderly people and chronically ill patients are at elevated risk for post-influenza pneumonia.<sup>14,15</sup> According to a prospective cohort study based on hospital-based influenza surveillance, most patients with post-influenza pneumonia (72.9%) are  $\geq$  65 years of age.<sup>14</sup> Among co-morbidities, chronic lung disease resulted in the highest risk for pneumonia development, with an odds ratio (OR) of 4.16 (1.98–8.75), followed by chronic renal disease (OR 2.96, 95% CI 1.12–7.87) and cerebrovascular disease (OR 1.61, 95% CI 0.70–3.69).<sup>14</sup> Moreover, the risk of post-influenza pneumonia was significantly increased according to the number of concurrent chronic medical conditions: two co-morbidities (OR, 6.9), three co-morbidities (OR, 7.1), or four co-morbidities (OR, 16.3).<sup>15</sup>

**Table 1.** Meta-analyses of influenza vaccine effectiveness against pneumonia- or influenza-related hospitalization in the elderly.

Author	Published year	Setting	Study design (No. of studies)	Subject age (years)	Pooled vaccine effectiveness, percent (95% CI)
Domnich et al. <sup>16</sup>	2017	Community and nursing home	Case-control (4)	≥ 65	49 (39 to 61) <sup>*</sup>
Darvishian et al. <sup>21</sup>	2014	Community	Cohort (8)	≥ 60	33 (23 to 43) <sup>†</sup>
Chan et al. <sup>17</sup>	2014	Nursing home	Cohort (3)	≥ 60	25 (6 to 40) <sup>‡</sup>
Jefferson et al. <sup>18</sup>	2010	Nursing home	Case-control (4)	≥ 65	37 (18 to 53)
		Community	Cohort (17)	≥ 65	46 (33 to 56)
Vu et al. <sup>19</sup>	2002	Community	Cohort (8)	≥ 65	27 (21 to 33)
		Community	Cohort (2)	≥ 65	33 (27 to 38)
Gross et al. <sup>20</sup>	1995	Community and nursing home <sup>§</sup>	Case-control (7)	≥ 65	53 (35 to 66)
			Cohort (9)	≥ 65	

\*Vaccine effectiveness of MF59-adjuvanted influenza vaccine.

†Vaccine effectiveness from conventional meta-analyses.

‡Vaccine effectiveness from meta-analyses adjusted for internal and external bias.

§Most studies consisted of institutionalized elderly except for one study.

### Effectiveness of influenza vaccine against pneumonia

Six meta-analyses were previously conducted to evaluate the effectiveness of influenza vaccine against pneumonia- or influenza-related hospitalization in the elderly (Table 1).<sup>16–21</sup> A meta-analysis by Dominich et al. assessed the effectiveness of MF59-adjuvanted influenza vaccine in the elderly.<sup>16</sup> All meta-analyses demonstrated that administering influenza vaccine was effective for preventing hospitalization due to pneumonia or influenza, although the estimates of effectiveness ranged from 25 to 53%. Some meta-analyses included only community-dwelling elderly individuals, while others also included institutionalized elderly individuals. The results of previous reviews suggest that the effectiveness of influenza vaccine against pneumonia- or influenza-related hospitalization is higher in the institutionalized elderly (36–47%) than in the community-dwelling elderly (25–33%).<sup>17–19,21</sup> Thus, the inclusion of heterogeneous study samples might affect results, resulting in variable vaccine effectiveness assessments between meta-analyses.

When we examined individual studies of the community-dwelling elderly, we found that the studies were conducted in geographically diverse areas during different influenza seasons (Tables 2 and 3).<sup>14,22–38</sup> The size of the influenza epidemic and the degree of vaccine mismatch varied widely by study setting. Thus, some studies showed good effectiveness of influenza vaccine against pneumonia, while others showed unfavorable results. In cohort studies, five among nine (55.6%) showed significant effectiveness of influenza vaccine for preventing

pneumonia- or influenza-related hospitalization (Table 2). The case-control studies also showed results similar to cohort studies; influenza vaccine was effective in six of nine studies (66.7%) and the effect was statistically significant (Table 3). Although meta-analyses and many observational studies have shown significant effectiveness for preventing pneumonia- or influenza-related hospitalization among vaccinated elderly people, most studies included severe acute respiratory infections (SARIs) and were not confined to pneumonia cases. In addition, most were conducted during past periods when influenza vaccine uptake rates were low and available anti-viral agents were limited. In a modern context, in which vaccine uptake rates are high, the herd effect may be more significant, and early antiviral treatment may therefore reduce the chance of progression to pneumonia among influenza-infected patients.<sup>6,39</sup> Further studies are required to better understand influenza vaccine effectiveness against pneumonia in a modern context, characterized by high vaccine uptake and antiviral use.

### Perspectives

Although vaccine effectiveness varies for seasonal influenza according to antigenic drift, trivalent inactivated influenza vaccine showed 59% efficacy (95% CI, 51–67%) against laboratory-confirmed influenza in randomized clinical trials.<sup>40</sup> In addition, trivalent inactivated influenza vaccine significantly reduced pneumonia- or influenza-related hospitalizations, with a vaccine effectiveness of 25–53% across meta-

**Table 2.** Cohort studies of influenza vaccine effectiveness (VE) for preventing pneumonia- or influenza-related hospitalization among the community-dwelling elderly.

Author	Publication year	Country	Study periods	Subject age (years)	Sample size	VE (95% CI)
Arriola et al. <sup>22</sup>	2017	United States	2013–2014	≥ 65	1,588	–2 (–27 to 19)
Arriola et al. <sup>25</sup>	2015	United States	2012–2013	65–74	1,296	20 (–6 to 39)
				≥ 75	2,680	–2 (–23 to 16)
Song et al. <sup>14</sup>	2015	South Korea	2013–2014	≥ 65	573	55 (29 to 71)
Simpson et al. <sup>26</sup>	2013	United Kingdom	2000–2009	≥ 65	1,358	12 (–2 to 24)
Baxter et al. <sup>27</sup>	2010	United States	1997–2008	≥ 65	4,018,380	9 (3 to 14)
Nichol et al. <sup>29</sup>	2007	United States	1990–2000	≥ 65	713,812	27 (23 to 32)
Nordin et al. <sup>30</sup>	2001	United States	1996–1997	≥ 65	124,582	20 (5 to 31)
			1997–1998	≥ 65	158,454	24 (14 to 34)
Nichol et al. <sup>32</sup>	1999	United States	1990–1996	≥ 65	147,551	39 (26 to 52)
Baker et al. <sup>38</sup>	1980	United States	1968–1969	≥ 65	9,760	2 (–23 to 13)
			1972–1973	≥ 65	10,740	74 (–8 to 94)

**Table 3.** Case-control studies of influenza vaccine effectiveness (VE) for preventing pneumonia- or influenza-related hospitalization among community-dwelling elderly.

Author	Publication year	Country	Study period	Subject age (years)	Sample size	VE (95% CI)
Grijalva et al. <sup>24</sup>	2015	United States	2010–2012	≥65	429	48 (–33 to 80)
Mahmud et al. <sup>23</sup>	2015	Canada	2009–2010	≥65	5,852	10 (–16–30)
Jackson et al. <sup>28</sup>	2008	United States	2000–2003	≥65	3,519	9 (–10 to 23)
Crocetti et al. <sup>21</sup>	2001	Italy	1994–1995	≥65	825	33 (5 to 52)
Puig-Barbera et al. <sup>33</sup>	1997	Spain	1994–1995	≥65	249	79 (45 to 92)
Ohmit et al. <sup>34</sup>	1995	United States	1990–1991 1991–1992	≥65	2,197 2,761	31 (4 to 51) 32 (7 to 50)
Mullooly et al. <sup>35</sup>	1994	United States	1981–1989	≥65, non-high-risk group ≥65, high-risk group	150,713 100,321	40 (1 to 64) 30 (17 to 42)
Fedson et al. <sup>36</sup>	1993	United States	1982–1983 1985–1986	≥65	10,471 9,720	37 (15 to 53) 39 (19 to 53)
Foster et al. <sup>37</sup>	1992	United States	1989–1990	≥65	2,507	33 (8 to 52)

analyses.<sup>16,18–21,41</sup> However, there are several limitations of the current influenza vaccines. Vaccine effectiveness is low in the elderly, who are at heightened risk for post-influenza pneumonia. Influenza vaccine lacks effectiveness in the elderly (aged ≥ 65 years) during seasons with antigenic mismatch.<sup>42</sup> It remains unclear whether the conventional influenza vaccine is effective for preventing pneumonia even during seasons with marked antigenic drift. Moreover, although the elderly are advised to undergo annual influenza vaccination, there is a concern of blunted antibody response after repeated vaccination, particularly against A/H3N2.<sup>43</sup> Further studies are required to clarify whether repeated influenza vaccination reduces antibody response and clinical effectiveness or not.

Considering the low effectiveness of conventional influenza vaccines in the elderly, several highly immunogenic influenza vaccines have been developed and are available in developed countries: MF59-adjuvanted influenza vaccine, ASO<sub>3</sub>-adjuvanted influenza vaccine, intradermal influenza vaccine and high-dose influenza vaccine (60 μg of hemagglutinin per strain). The MF59-adjuvanted vaccine showed superior relative effectiveness (25–63%) to unadjuvanted conventional vaccines for preventing hospitalizations due to pneumonia/influenza.<sup>16,44,45</sup> Similarly, patients receiving the high-dose vaccine had significantly lower risk of developing laboratory-confirmed influenza infections (relative risk 0.76, 95% CI 0.65–0.90) compared to those receiving the standard-dose vaccine.<sup>46</sup> In addition, quadrivalent influenza vaccines have shown superior immunogenicity against the B lineage not included in trivalent influenza vaccines.<sup>47</sup> Quadrivalent influenza vaccines are expected to reduce influenza disease burden and to be cost-effective in the elderly compared with trivalent influenza vaccines.<sup>48,49</sup> Thus, further evaluations of the comparative effectiveness of diverse vaccine formulations for preventing influenza infection, post-influenza pneumonia and related hospitalization/mortality are warranted. Based on the desire to maximize cost-effectiveness and budget impact, influenza vaccination strategies should be tailored in the elderly.

### Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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