

## ONLINE FIRST

## Influenza Vaccines

## Time for a Rethink

**N**EARLY EVERY INFLUENTIAL professional society has endorsed the Centers for Disease Control and Prevention (CDC) recommendation of influenza vaccine for all people 6 months and older. Beyond reviewing the vaccines' contraindications, why might a practicing physician want to do their own homework on the benefits and risks of influenza vaccines? The answer is that the disease is less fearful than advertised, the vaccines are less beneficial than believed, and the harms of vaccines are not easily dismissed.

## WHY NOT?

First, influenza vaccines have a zero chance of benefitting most recipients, since the majority of Americans do not annually contract influenza. A recent Cochrane systematic review found that between 33 and 100 healthy adults would need to be vaccinated to avoid the onset of influenza symptoms in 1 individual.<sup>1</sup> Furthermore, decisions over influenza vaccination should be considered in the context of the likely case that the public assumes that so-called flu shots are designed to prevent "flu" and its complications. However "flu," better known as influenza-like illness, while arguably a very patient-centered and clinically relevant syndrome, has hundreds of known and unknown causes, of which influenza is just one. A reanalysis of the placebo and do-nothing arms of 88 vaccine studies suggested that the proportion of influenza-like illness caused by influenza is on average 7%.<sup>2</sup> While promotional materials typically refer to influenza as "flu,"<sup>3</sup> potential vaccine recipients should be educated

about the distinction and its relevance to influenza vaccine performance against outcomes they wish to avoid.

Second, a key objective of influenza vaccine campaigns today (and in decades past) is to reduce mortality or serious complications of influenza, particularly among the elderly population, in which most of the serious outcomes occur. However despite more than 50 years of recommended use in the elderly, it remains unclear if the vaccine can deliver those benefits.<sup>4</sup> In the last 4 decades, just 1 randomized controlled trial has successfully assessed influenza vaccines in the elderly population living in the community, but only 10% of participants were 75 years or older, and the trial was underpowered to detect differences in hospitalization or mortality.<sup>5</sup> Officials at the CDC have thus supported their policy by citing evidence from published, non-randomized retrospective cohort studies,<sup>6,7</sup> which have reported "large reductions in hospitalizations and deaths among the vaccinated elderly"<sup>8(p15)</sup>—including a 48% reduction in all-cause mortality. The problem is that if such effects were real, the historical increase in vaccine uptake among the elderly population should readily have resulted in decreased total winter mortality, but it has not.<sup>9</sup> As other researchers have demonstrated in studies that found similarly massive reductions in mortality, particularly during months when influenza was not circulating,<sup>10-12</sup> and the CDC now acknowledges,<sup>8</sup> the retrospective studies may be heavily confounded by healthy user bias (the tendency for healthier people to be more likely than less healthy people to get vaccinated). Given current poor vaccine performance, influenza does not deserve

to be called a "vaccine-preventable disease."

Third, evidence is lacking to support the expectation that vaccination of healthy health care workers will reduce the spread of influenza and its complications to particularly vulnerable elderly patients. While multiple published studies report impressive benefits in such scenarios (including 2 cited by the CDC in support of its recommendation of health care worker vaccination<sup>13,14</sup>), a Cochrane review of these studies noted that their results defy logic: the vaccine appeared to reduce death from all causes but not death from influenza. The Cochrane reviewers judged the studies to be "at high risk of bias," and concluded that there is "no evidence that only vaccinating healthcare workers prevents laboratory-proven influenza, pneumonia, and death from pneumonia in elderly residents in long-term care facilities."<sup>15(p2)</sup>

## BETTER THAN NOTHING?

It is tempting to think that vaccination still represents an intervention whose benefit—even if smaller than thought and based on poor-quality evidence—is still better than nothing. Even among groups that have acknowledged the aforementioned facts I listed, many remain supportive of CDC's universal vaccination policy.<sup>16,17</sup> But this position necessarily makes light of potential vaccine-related harms.

Cochrane reviews have noted serious deficiencies in safety outcome reporting in published influenza vaccine trials,<sup>1,4,18</sup> suggesting a lack of understanding of the true safety profile of influenza vaccines that hampers an ability to weigh potential benefits against harms. While Guillain-Barre Syndrome has been



the most widely discussed influenza vaccine-related harm following its dramatic appearance during the 1976 "swine flu" scare, it is not the only risk associated with influenza vaccine. In 2009, Australia suspended its universal vaccination program for children younger than 5 years because of a surge in febrile convulsions following vaccination (1 in 110 children).<sup>19</sup> Also in 2009, cases of narcolepsy following vaccination in adolescents were reported in Finland and Sweden. Official inquiries into these events have confirmed influenza vaccine's role in all 3 countries, with the precise biological mechanisms still not understood.<sup>20-22</sup> In Canada, epidemiologic investigations indicate that persons who received a seasonal influenza vaccine in 2008 had an increased risk of acquiring "pandemic" H1N1 in 2009<sup>23</sup> (perhaps by inhibiting antibodies relevant to heterosubtypic immunity<sup>24</sup>)—important considering H1N1 vaccine generally arrived past most epidemic peaks. These events received scant coverage in the American scientific and lay presses.

The adverse events of 2009 arguably only came to light because their incidence was approximately 10 times the background rate, and surveillance systems were heightened because of concerns over H1N1. We must always remember that influenza vaccines are biologicals, and biological manufacturing is messy, with risks of contamination far in excess of drug production. For biologicals produced anew each year, these unfortunate events demonstrate that good past experience is not necessarily predictive of future vaccine safety.<sup>25</sup>

Other researchers have reported that annual influenza vaccination hampers development of CD8 T-cell immunity in children.<sup>26</sup>

At a societal level, successful public health campaigns are only possible (and ethical) with the cooperation and buy-in of the public they serve. But as current influenza vaccine campaigns are based on information asymmetries—in which the public's understanding of potential vaccine benefit and potential harms is incompatible with the evidence—the public trust is risked by a con-

tinuation of the status quo.

## THE GOOD NEWS

Lost amidst the hum of annual influenza vaccine campaigns is the basic fact that influenza vaccines target a disease that is, for most people, self-limiting. While unpleasant, today, tragedies are rare. And for those who wish to be proactive, systematic reviews of nonpharmaceutical interventions—largely based on studies of severe acute respiratory syndrome—have shown impressive evidence that measures like handwashing and wearing masks and gowns reduce the incidence of respiratory diseases.<sup>27</sup> Large head-to-head trials comparing vaccines against measures such as handwashing are needed.

To summarize, the evidence that influenza represents a threat of public health proportions is questionable, the evidence that influenza vaccines reduce important patient-centered outcomes such as mortality is unreliable, the assumption that past influenza vaccine safety is predictive of future experience is unsound, and nonpharmaceutical interventions to manage influenza-like illness exist.

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