

## Influenza and Cardiovascular Disease

### A New Opportunity for Prevention and the Need for Further Studies

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In the United States, 12 400 000 people live with a history of heart attack, angina pectoris, or both. Of this population, an estimated 1 100 000 will suffer a new or recurrent coronary attack this year.<sup>1</sup> According to the World Health Organization, cardiovascular disease (CVD) will be the leading cause of death worldwide by 2020.<sup>2</sup>

#### Infections and Atherosclerosis

Infectious agents have been implicated in the etiology of atherosclerosis and its complications since the early 1900s.<sup>3</sup> Clinicians have long noticed that  $\approx 30\%$  of myocardial infarctions (MIs) are preceded by an upper respiratory infection.<sup>4,5</sup>

Agents implicated in atherosclerosis include cytomegalovirus (CMV), *Chlamydia pneumoniae*, Herpes simplex viruses 1 and 2 (HSV-1 and HSV-2), *Helicobacter pylori*, *Mycoplasma pneumoniae*, *Porphyromonas gingivalis*, and Enterovirus.<sup>6-13</sup> Antibiotic therapy for *C. pneumoniae* in CVD patients has been tried with transient or no benefit to date.<sup>14,15</sup> Ongoing studies may give a definitive answer by late 2003.<sup>16</sup>

Here, we review recent studies suggesting influenza may play a role in atherogenesis or atherothrombosis. In 2000, we reported a case-control study in patients with known coronary artery disease; influenza vaccination was associated with a 67% reduction (OR 0.33, 95% CI 0.13 to 0.82,  $P=0.017$ ) in risk of MI in the subsequent influenza season.<sup>17</sup> In a simultaneous population-based case-control study, Siscovick et al<sup>18</sup> found that after adjusting for demographic, clinical, and behavioral risk factors, influenza vaccination was associated with a 49% reduction (OR 0.51, 95% CI 0.33 to 0.79) in risk of out-of-hospital primary cardiac arrest. Another case-control study reported a 50% risk reduction (OR 0.50, 95% CI 0.26 to 0.94,  $P=0.033$ ) in stroke risk in subjects vaccinated during the year of the study and a 48% (OR 0.42, 95% CI 0.21 to 0.81,  $P=0.009$ ) risk reduction in those vaccinated during the last 5 years.<sup>19</sup>

In a recent study by Jackson et al<sup>20</sup> on a cohort of survivors from a first MI, influenza vaccination was not associated with reduced risk of recurrent coronary events during the corre-

sponding period of November through October (adjusted hazard ratio 1.18, 95% CI 0.79 to 1.75). The study by Jackson et al<sup>20</sup> was conducted in a cohort of health maintenance organization patients who may have received better health care than patients in other studies. In this study, 74% of subjects received at least 1 influenza vaccine during the follow-up period (43% to 66% per year), which is much higher than the national average ratio ( $\approx 30\%$ ). Also, some subjects may have been misclassified owing to out-of-network vaccination. Other limitations of the study are the relatively low number of MIs in patients over 65 years of age, excluding those who had fewer than 4 outpatient visits and excluding the early 90-day period after the acute MI (when patients are at highest risk of secondary events). Finally, the CIs around the point estimates were not narrow, which does not permit ruling out a clinically important effect.<sup>20</sup>

Recently, Nichol et al<sup>21</sup> reported their study on cohorts of community-dwelling elderly subjects (288 238 persons  $\geq 65$  years old) during 2 influenza seasons. In their observational study, vaccination against influenza was associated with a reduction in the risk of hospitalization for cardiac disease (reduction of 19%,  $P<0.001$ ), cerebrovascular disease (reduction of 16% to 23%,  $P<0.018$ ), and all-cause mortality (reduction of 48% to 50%,  $P<0.001$ ).

In a randomized clinical trial, Gurfinkel et al<sup>22</sup> showed that cardiovascular death occurred in 2% of patients in the vaccine group compared with 8% in the control group (relative risk [RR] 0.25, 95% CI 0.07 to 0.86,  $P=0.01$ ). The triple composite end point occurred in 11% of patients in the vaccine group compared with 23% of controls ( $P=0.009$ ).<sup>22</sup> They have continued their clinical trial and found that the incidence of cardiovascular death at 1 year was significantly lower among patients who received vaccination (6%) than among controls (17%; RR 0.34, 95% CI 0.17 to 0.71,  $P=0.002$ ; Dr Enrique Gurfinkel, personal correspondence, 2002).

#### How Might Influenza Trigger Acute MI?

Infectious agents have different effects on pathophysiology of atherosclerosis and its clinical complications.<sup>23</sup> Whereas the

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Guest Editor for this article was Paul M Ridker, MD, MPH, Brigham & Women's Hospital, Boston, Mass.

Presented in part at the First Symposium on Influenza and Cardiovascular Disease: Science, Practice, and Policy held at Texas Heart Institute, Houston, Tex, April 26, 2003.

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(*Circulation*. 2003;108:2730-2736.)

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*Circulation* is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000102380.47012.92

majority of the suspected infectious agents play their atherogenic role by initiating or aggravating a chronic vascular or systemic inflammatory process, influenza may have a rather different effect by triggering destabilization of already present vulnerable plaques.

To test the effect of influenza on atherosclerosis, we inoculated atherosclerotic apolipoprotein E-deficient mice with influenza A and found a marked increase in inflammation and thrombosis in plaques but not in normal regions of the aorta.<sup>24</sup> Potential mechanisms may include (1) antigenic cross-reactivity (in our mice, only the plaques, and not the normal arterial segments, were inflamed); (2) an increase in pro-inflammatory, prothrombotic cytokines; (3) endothelial dysfunction; (4) increased plasma viscosity; (5) tachycardia; (6) release of endogenous catecholamines; (7) psychological distress; (8) dehydration leading to hypotension and to hemoconcentration; (9) hypoxemia; (10) demand ischemia; (11) loss of the anti-inflammatory properties of HDL particles; (12) increase in trafficking of macrophages into the arterial wall; (13) pronounced expression of inflammatory cytokines by infected monocytes and reduction in clotting time; and (14) induction of procoagulant activity in infected endothelial cells, reduction in the clotting time, and increase in the expression of tissue factor.<sup>17,25–28</sup>

In addition to the acute effects, influenza may have indolent and chronic inflammatory consequences in the body. A state of chronic alveolitis has been described in mice with ongoing inflammatory response and presence of antigen in lungs for months (up to 1 year) after acute influenza.<sup>29</sup>

Bouwman et al<sup>27</sup> recently showed that infection of monocytes by influenza reduced clotting time by 19%. Monocytes produced both interleukin (IL)-6 and IL-8 after infection with influenza (3- to 5-fold higher than with CMV and *C. pneumoniae*). The anti-inflammatory cytokine IL-10 was not produced by infected monocytes. This pronounced expression of inflammatory cytokines may induce local and/or systemic inflammatory reactions, which may be associated with plaque rupture and atherosclerosis.<sup>27</sup>

Influenza activity has been suggested as an explanation for the winter peak of MI.<sup>5,30,31</sup> Glezen and colleagues,<sup>32</sup> in a study in Houston from 1975 to 1977, found the incidence rates of death due to ischemic heart disease, hypertension, and cerebrovascular disease were similar to that of death attributed to influenza and pneumonia, with peaks and troughs that lagged influenza activity by  $\approx 2$  weeks.

Azambuja and Duncan<sup>33</sup> in an ecological study showed an association between the age distribution of mortality due to influenza and pneumonia associated with the US influenza pandemic in 1918 to 1919 and the distribution of coronary heart disease (CHD) mortality from 1920 to 1985 in survivors from the corresponding birth cohorts. They have suggested that the 1918 influenza pandemic (and probably the subsequent epidemics) might have played a role in the epidemic of CHD mortality in the 20th century. This work needs further validation and proposes a new mechanism for the effect of influenza on CHD, probably due to antigen mimicry and initiation of autoimmune reactions known to be important in atherosclerosis.<sup>34</sup>

### The Need for More Studies

The 3 database studies have the limitations inherent to their case-control design (best suited for generating hypotheses) and small sample sizes. However, 4 such studies with uniformly large ORs, plus 1 randomized trial and biological plausibility, suggest that further research is needed to explore the possibility of a cause-and-effect relation.

Observational studies of preventive therapies may reflect a “healthy user” effect. However, all these studies have considered this possibility. Naghavi et al<sup>17</sup> adjusted for CHD risk factors and treatments and further controlled for multivitamin use and exercise (behaviors associated with education and health consciousness). They<sup>17</sup> also forced their regression model to include a history of vaccination in previous years. Siscovick et al<sup>18</sup> adjusted for 12 potential confounders and concluded that the magnitude of the observed effect made it unlikely that uncontrolled confounders could have accounted for their findings. Lavallée et al<sup>19</sup> adjusted for 12 traditional risk factors for stroke and other potential confounding factors and further adjusted for the use of antibiotics during the past 3 months or history of a blood cholesterol assay (both likely to reflect general health behavior). The results of these studies remained significant after the above-mentioned adjustments. As discussed, the effect of uncontrolled confounders cannot be completely ruled out in case-control studies, and only randomized clinical trials can give a clear-cut answer.<sup>22</sup>

Are new trials needed? After all, it is already clear that influenza vaccines save lives. One answer is that prevention of MI may be important enough to some people to motivate them to be vaccinated. The latest and broadest guidelines of the Centers for Disease Control (CDC) state that “influenza vaccine is strongly recommended for any person aged  $>6$  months who — because of age or underlying medical condition — is at increased risk for complications of influenza.”<sup>35</sup> This group includes persons over 50 years of age and people with chronic CVD. Even with the prior (more limited) indications for influenza vaccination, many eligible persons were not vaccinated; in 1998, the influenza vaccination rate among persons aged  $>65$  years was only 66% among non-Hispanic whites, 50% for Hispanics, and 46% among non-Hispanic blacks. For all adults aged 18 to 64 years with high-risk conditions, the vaccination rate was 31%, and it was 23% for adults under 50 years of age (and 27% [age-adjusted, 1999] for persons with heart disease), which is far short of the Healthy People 2000 goal of 60%.<sup>35</sup> We speculate that the increased mortality (cardiovascular and all cause) of disadvantaged minorities could be attributed in part to this difference in vaccination rates.

Another important reason to confirm and quantify the cardiovascular benefit is that it could lead to more accurate recommendations, for example, to vaccinate persons at risk of MI on the basis of the presence of CVD risk factors. Such persons are numerous, yet according to the current recommendations of the CDC, even someone with all CVD

risk factors would not be vaccinated unless they were over 50 years of age or were known to have heart disease.

Third, trials may shed light on the mechanisms by which influenza triggers cardiovascular complications. For example, trials may determine whether some strains may be more prone than others to precipitate cardiovascular events. Such data may assist in vaccine formulation. Trials may also reveal whether cardiovascular complications are more closely linked to the immune response or to the magnitude of the infection per se. This will have implications as to whether aspirin (in adults) or newer immunomodulating drugs are helpful or harmful. Data collected during trials may clarify whether influenza can cause an indolent infection or, alternatively, promote atherosclerosis by chronic postinfectious autoimmune response, as with poststreptococcal glomerulonephritis and rheumatic fever.

Fourth, trials may show that influenza vaccination saves more lives than previously suspected. Influenza epidemics have been estimated to cause an average of 20 000 deaths per year in the United States.<sup>36</sup> But if influenza vaccine can indeed reduce coronary mortality and stroke by 50%, then we estimate that vaccination could potentially save as many as 91 000 lives per year (see below). Can these estimates be reconciled? It is conceivable that doctors tend to fill out death certificates according to their expectations; accordingly, deaths due to cardiac arrest are usually attributed to MI or ventricular fibrillation. If the patient had a mild case of influenza a few days before, this could be overlooked. Thus, the death is not considered flu related, which would underestimate the number of deaths triggered by influenza and the lives saved by the vaccine. Indeed, in 1 study, only 24% and 61% of deaths due to pneumonia and influenza would have been included in related mortality statistics by the National Center for Health Statistics and CDC, respectively.<sup>37</sup> Finally, the large effects found in the cardiovascular studies are supported by studies of all-cause mortality, as discussed below.

### Influenza Vaccination and All-Cause Mortality

In an analysis of 6 cohorts, influenza vaccination has been associated with a 50% reduction in all-cause mortality in healthy senior citizens.<sup>38</sup> In 259 627 people 65 years or older in a Swedish cohort, influenza vaccination (in conjunction with pneumococcal vaccine) led to a 57% decrease in total mortality.<sup>39</sup> A limited case-control study reported a 41% decrease in mortality of people aged 16 years or older.<sup>40</sup> A case-control study in persons 45 years or older suggested a 30% reduction in death due to all causes.<sup>41</sup> Vaccination of health workers caring for the elderly population residing in nursing homes has been associated with up to a 50% reduction in mortality of the elderly.<sup>42</sup> In a meta-analysis of 20 cohort studies, influenza vaccination led to a 68% reduction in death; vaccine efficacy in the case-control studies was  $\approx 30\%$  for preventing deaths due to all causes.<sup>43</sup>

The  $\approx 50\%$  reduction in all-cause mortality is in line with our findings and those of the other case-control studies of marked reduction in cardiovascular events.<sup>17-19</sup>

### Estimate of Lives Saved by Influenza Vaccination

#### Assumptions

$$\begin{aligned} M &= 729\,000^1 \\ R &= 50\%^{17-19} \\ S &= 0.25 \\ A &= 10\% \text{ to } 20\%^{45,46} \end{aligned}$$

#### Estimation\*

$$D = M \times R \times S$$

#### Calculation

$$D = M \times R \times S = 729\,000 \times 0.50 \times 0.25 = 91\,125$$

#### Alternate estimation (considering the attack rate)†

$$D = M \times R \times A$$

#### Alternate calculation

$$D = M \times R \times A = 729\,000 \times 0.50 \times (0.10 \text{ to } 0.20) = 36\,450 \text{ to } 72\,900$$

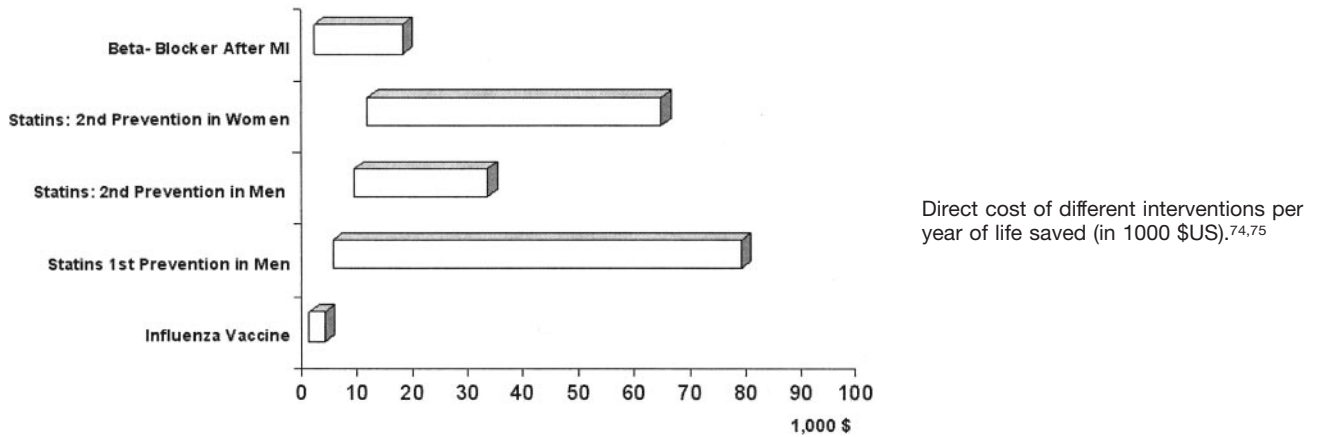
D indicates reduction in cardiovascular death resulting from influenza vaccination; M, mortality due to CVD each year; R, reduction in CVD mortality that ensues from influenza vaccination; S, limitation of effect of vaccine to influenza season ( $\approx 3$  months [one fourth] of year); and A, annual attack rate of influenza in adults.

\*For estimates based on randomized controlled trials and case-control studies of influenza vaccine, we divided by 4 to reflect the average 3-month duration of influenza epidemics. This ignores any possible baseline influenza cases and indolent or subclinical cases. It also ignores the winter peak in CVD mortality. This estimation may cause the impact of influenza vaccination to be underestimated.

†One-fourth correction factor is not used in alternative calculation because the duration of influenza season is already accounted for by the attack rate.

Each year, a total of 729 000 Americans die of coronary heart disease and stroke.<sup>1</sup> If further studies confirm a 50% reduction in CVD deaths, then influenza vaccination could save  $\approx 91\,000$  lives per year (Table). Although this number seems preposterous, these estimates ignore the possibility that influenza vaccine prevents death outside the traditional influenza season. Also omitted are the potential cardiovascular deaths prevented by neuraminidase inhibitors. Furthermore, many deaths may already be prevented by influenza vaccine (ie, 91 000 lives is the upper limit of additional lives that may be saved by successful universal vaccination). Indeed, the increase in use of the influenza vaccine over the past 20 years may explain a portion of the decline in CHD, which to date has not been fully understood.<sup>44</sup> A more conservative estimate, based on the estimated attack rate of influenza in the United States each year ( $\approx 10\%$  to  $20\%$  of the adult population),<sup>45,46</sup> leads to an estimated 36 450 to 72 900 lives saved per year (Table). The 2 sets of assumptions yield different calculations, but each substantially exceeds the previous estimated 20 000 deaths per year.

Even the more conservative estimates exceed by several fold the oft-cited report by Simonsen et al,<sup>36</sup> which used a mathematical model to estimate an average of 20 000 excess annual US deaths due to influenza epidemics. That estimate was based on the difference between observed mortality in the time periods with and without an influenza epidemic. This method may underestimate the number of deaths due to non-epidemic flu and due to atypical, undiagnosed, and unreported cases. Also, the baseline expected



number of deaths may be artifactually high, such that epidemics with low mortality go undetected.<sup>46</sup> Even in that model, the average number of excess deaths per year was 29 000 in the last 8 years (versus 15 542 in the first 12 years).<sup>47</sup> Moreover, the “gold standard” of influenza diagnosis is uncertain, because it is defined by concordance of clinical symptoms, epidemic reporting, immunoassays, and viral cultures, all of which may be insensitive. Finally, these criteria do not include the possibility that influenza can trigger a persistent autoimmune inflammation of the atherosclerotic plaque analogous to the chronic alveolitis described in mice.<sup>29</sup> Thus, randomized trials and case-control studies that suggest influenza vaccine may save 36 000 to 91 000 lives (in the United States per year from CVD), in addition to those saved from death due to heart failure and pneumonia, for example,<sup>48</sup> cannot be dismissed.

### Cost-Effectiveness

Influenza vaccine is cost-effective and for some groups may actually be cost-saving (ie, costing less to perform than not to perform when taking into account all the costs of influenza and its complications).<sup>35,49</sup> In persons aged >65 years, vaccination has been shown to be cost-saving and associated with reductions in hospitalization and death.<sup>38,50,51</sup> In adults aged <65 years, vaccination can reduce both direct medical costs and indirect costs from work absenteeism.<sup>52–54</sup> In a randomized, placebo-controlled clinical trial in healthy, working, 18- to 64-year-old adults, Nichol et al<sup>52</sup> estimated the cost savings to be \$46.85 per person vaccinated. However, some other studies in younger populations, although showing remarkable health benefits, failed to demonstrate economic benefits, especially in the years when there was a mismatch between the vaccine and the circulating viruses.<sup>54–56</sup> These findings support a strategy of routine annual vaccination for this group, especially when vaccination occurs at efficient and low-cost sites.

By comparison, it is estimated that if 10 million people at risk of vascular disease worldwide begin statin treatment today, some 50 000 lives would be saved. Noting that statins reduce CVD death by 30% on average, use of the influenza vaccination may in theory save more lives with lower cost (\$10 to \$12 per year) than statins ( $\approx$ \$1000 a

year). Thus, influenza vaccination may be one of the most cost-effective interventions for cardiovascular patients (Figure).

### Potential Adverse Effects

Influenza vaccination is generally safe. In a randomized, double-blind, crossover trial in the elderly, Margolis and colleagues<sup>57</sup> reported no significant systemic symptoms. In another randomized clinical trial, Govaert et al<sup>58</sup> found no increase in systemic adverse reactions, only an increase in local side effects.

There has been a debate over a link between influenza vaccination and Guillain-Barre syndrome (acute ascending polyneuritis; GBS).<sup>35,59</sup> In the autumn of 1976, there was an unexpected increase (by a factor of 4 to 8) in the number of cases of GBS after use of a “swine flu” vaccine.<sup>60,61</sup> However, there are questions about its methodology, such as lack of validation of the negative-vaccination responses and nonsignificant findings for people aged  $\geq 65$  years. Furthermore, this relation was not confirmed in other studies and has not been reported with other types of influenza vaccines.<sup>62,63</sup> In the US Army’s mass influenza vaccination program (1980–1988), there was no increase in incidence of GBS.<sup>64</sup>

Recommendations of the Advisory Committee on Immunization Practices (ACIP) conclude that to date, there is no indication of a substantial increase in GBS associated with influenza vaccines (other than the swine influenza vaccine in 1976), and that if influenza vaccine does pose a risk, it is probably slightly more than 1 additional case per million persons vaccinated. The potential benefits of influenza vaccination outweigh the possible risks for developing vaccine-associated GBS.<sup>35</sup>

However, given that the immune response to the virus may well contribute to influenza-triggered cardiovascular events, future trials should examine whether the vaccine may also trigger a small number of events. Of some reassurance is the fact that cells exposed to the avian-human H1N1 reassortant vaccine showed increased synthesis of viral neuraminidase, previously reported to induce fever-producing cytokines, but no detectable increase in production of IL-1 $\beta$ , IL-6, and tumor necrosis factor- $\alpha$  or decrease in IL-1 inhibitor activity.<sup>65</sup>

## Recommendations

### *Improve Adherence to Existing Guidelines*

Current CVD prevention guidelines do not mention influenza vaccination.<sup>66–70</sup> We suggest that the American Heart Association, European Society of Cardiology, American College of Cardiology, and other cardiovascular groups endorse the CDC's recommendation of vaccination of all persons over 50 years of age and of all with CVD. Because vaccination rates are lowest among the less affluent, local and federal education programs should target those groups. Financial incentives might also be considered.

### *Clinical Trials of Vaccine and Antivirals for Preclinical CVD*

We urge these groups, plus the CDC, the National Heart, Lung, and Blood Institute, and the American Public Health Association, to advocate trials of vaccine for those with preclinical disease. Such trials might include patients with multiple risk factors, coronary calcification, borderline stress tests, or some combination of these. To ensure safety, these trials should also search for a possible early cardiovascular hazard, eg, MI precipitated by the vaccine, because there might be a group in whom the long-term cardiovascular benefit will be offset, such as patients with unstable angina.

Some trials should also include an arm in which household contacts are vaccinated. In Japan, a program of vaccination of schoolchildren against influenza resulted in a decrease in the incidence of influenza and mortality attributed to it among older persons.<sup>71</sup> Of interest, seasonal variability in mortality due to cardiovascular and respiratory disease and all causes plummeted and peak excursions were attenuated for the years this program was continued.<sup>72</sup>

Trials should also address the potential cardiovascular benefit of the new neuraminidase-inhibiting therapies such as Relenza (zanamivir) and Tamiflu (oseltamivir) when those with preclinical atherosclerosis have symptoms of or exposed to influenza. These drugs could prevent cardiovascular deaths in persons who do not receive the influenza vaccine, who are vaccinated but are nevertheless attacked by a strain of influenza not included in that year's vaccine, or whose immune response to the vaccine is inadequate. Such trials might also bank blood samples for subsequent genotyping and phenotyping of immune responses that may lead to better delineation of who is at risk of influenza-induced cardiovascular events and ways to prevent such events. The effect of influenza vaccination on the coagulation system, systemic and local inflammation, and intermediate and surrogate markers for subclinical atherosclerosis should be investigated in prospective cohort studies and clinical trials.

### *Increase Surveillance to Determine Which Influenza Strains Trigger Cardiovascular Events*

The CDC and the 3 remaining manufacturers of influenza vaccine can play other important roles as well, such as monitoring whether some influenza strains pose more cardiovascular risk than others and ensuring that influenza vaccine will be available every fall; in 2001, as in 2002, the vaccine was delayed. The average interval between influenza pandemics is  $\approx 20$  years (range 10 to 30 years), and it has now

been 34 years since the last pandemic.<sup>73</sup> New syndromic surveillance and "situation awareness" systems that use nontraditional data sources and state-of-the-art knowledge and information management techniques are needed to detect epidemics and pandemics at the earliest time and adjust response elements with dynamics of the events in a timely manner.

### *Promote Patient Education*

If further study confirms the cardiovascular risk of influenza, it will prompt clinicians and public health officials to increase efforts to educate influenza sufferers to rest, take an aspirin (for adults, and nonaspirin nonsteroidal anti-inflammatory drugs for children) and fluids, and not ignore chest discomfort and to reinforce to everyone the need for hand washing.

In summary, there is mounting evidence that influenza can trigger MI, stroke, and sudden death and that it accounts for many more deaths than previously estimated. Reexamination of existing data sets and new trials are needed to confirm these studies. Such trials will increase our understanding of atherogenesis and also suggest cost-effective strategies for vaccination, antiviral treatment, and public education. We predict that broadened indications for influenza vaccination and treatment, together with targeted prevention efforts, will save many persons with cardiovascular risk factors and/or CVD, at little cost.

## Acknowledgments

This work was supported in part by the US Army's Disaster Relief and Emergency Medical Services (DREAMS) grant #DAMD 17-98-1-8002. The authors wish to thank Drs R. Palmer Beasley, Keiji Fukuda, W. Paul Glezen, Pedro A. Piedra, Thomas A. Reichert, and Lone Simonsen for helpful discussions.

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KEY WORDS: infection ■ myocardial infarction ■ atherosclerosis ■ prevention ■ heart diseases

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*Circulation*. 2003;108:2730-2736; originally published online November 10, 2003;  
doi: 10.1161/01.CIR.0000102380.47012.92

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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