

ed by Bainton et al. (1978) as a possible link between influenza and myocardial infarction, could be explored using modern epidemiological and experimental methods.

After an absence of 21 years, H1N1 viruses reappeared in the United States in 1977, infecting mostly college-aged individuals. It would be interesting to follow the incidence of CHD-associated events in this cohort of exposed subjects to confirm (or rule out) the association found by Azambuja & Duncan. Moreover, the availability of vaccines and amantadine or rimantadine prophylaxis provides the basis for clinical trials to address this topic.

- BAINTON, D.; JONES, G. R. & HOLE, D., 1978. Influenza and ischaemic heart disease – A possible trigger for acute myocardial infarction? *International Journal of Epidemiology*, 7:231-239.
- DANESH, J.; WHINCUP, P.; WALKER, M.; LENNON, L.; THOMPSON, A.; APPLEBY, P.; GALLIMORE, J. R. & PEPYS, M. B., 2000a. Low grade inflammation and coronary heart disease: Prospective study and updated meta-analyses. *BMJ*, 321:199-204.
- DANESH, J.; WHINCUP, P.; WALKER, M.; LENNON, L.; THOMPSON, A.; APPLEBY, P.; WONG, Y. K.; BERNARDES-SILVA, M. & WARD, M., 2000b. *Chlamydia pneumoniae* IgG titres and coronary heart disease: Prospective study and meta-analysis. *BMJ*, 321:208-213.
- GRAYSTON, J. T., 2000. Background and current knowledge of *Chlamydia pneumoniae* and atherosclerosis. *Journal of Infectious Diseases*, 181(Sup. 3):S402-S410.
- JAVIER NIETO, F., 1998. Infections and atherosclerosis: New clues from an old hypothesis? *American Journal of Epidemiology*, 148:937-948.
- MUHLESTEIN, J. B., 2001. Chronic infection and coronary heart disease. *Medical Clinics of North America*, 84:123-148.
- ZHU, J.; JAVIER NIETO, F.; HORNE, B. D.; ANDERSON, J. L.; MUHLESTEIN, J. B. & EPSTEIN, S. E., 2001. Prospective study of pathogen burden and risk of myocardial infarction or death. *Circulation*, 103:45-51.

Guilherme L. Werneck

Pós-Graduação em Saúde Coletiva, Núcleo de Estudos de Saúde Coletiva, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil.

In their insightful paper, Maria Inês Azambuja & Bruce Duncan consider the possibility that, at least in part, the pathogen burden of H1N1 influenza infection might have been an important determinant in the rise and fall of coronary heart disease (CHD) mortality observed in the 20th century. Although I consider the paper well-founded, with plausible arguments, the empirical evidence is not very convincing to me. My comments are general thoughts that may hopefully contribute to the design of new studies on the topic, which I agree is important and deserves further consideration.

The authors drawn on two major pieces of empirical evidence to supporting their hypothesis: (1) the similarity between the relative mortality associated with the 1918-1919 influenza pandemic and the distribution of CHD deaths in the period 1920-1985, across successive birth cohorts; and (2) the ecological association between an indirect measure of longer persistence of H1N1 influenza virus and delayed onset of decline in CHD death rates.

Concerning the first piece of empirical evidence, at least two questions might be raised:

- Part of the “drop” in CHD mortality that we see in the graph is actually derived from the fact that more recent cohorts have not actually finished evolving over time. Therefore, there are successive missing bars of mortality for the older ages in the more recent cohorts, which, if included, would make the decline less sharp.
- It does not seem to me that the increase in CHD mortality among younger individuals, which really appears to “follow” the influenza pandemic mortality, tends to return to the levels expected for a population not exposed to the burden of influenza.

Regarding the second piece of evidence, the ecological correlation is based only on nine areas, at least one of which may be an extreme observation. To get a feeling of the uncertainty underlying the data, we approximated the values by inspecting the graph, and performed a simple exercise of estimating a series of Spearman correlation coefficients for random samples of the data (with replacement, using bootstrap): in more than 40% of the samples, the Spearman correlation coefficient was not statistically significant at the 0.05 level.

I wish to congratulate the authors for sharing their provocative thoughts with us. If more robust evidence could be gathered, they might provide important clues regarding CHD epidemiology and be useful for public health purposes.