there are reports of more than 300,000 excess deaths attributed to the flu epidemic. The same occurred in European countries, where historical data are usually available. Thus, it would be interesting to replicate similar analysis to data from other countries to learn whether a similar pattern of CHD mortality across birth cohorts, in accordance with mortality from influenza in the same cohorts, corroborate their study's findings.

Finally, as the authors made clear, the study presented here is a correlational one with the clear purpose of raising new hypotheses to be further evaluated using different epidemiological designs. According to Hennekens & Buring (1987), the chief limitation of such studies is their inability to link exposure to diseases in particular individuals, in other words, correlation data represent average exposure levels rather than individual values. Thus, it could be that individuals unexposed to the influenza virus were the ones who later died of CHD, that is, the so-called *ecological fallacy*. A second major limitation of correlational studies, as recognized by the Authors, is the inability to control for the effects of potential confounding factors.

Notwithstanding such considerable limitations, Azambuja & Duncan were brave in facing the challenge of introducing a new pioneering theory.

As such, it is worth quoting Andrew J. Hall (2001:1197-1198), commenting on another pioneering article: "*the study illustrates another saying of Geoffrey Rose: an epidemiologist needs dirty hands and a clean mind*". Dirty hands from collecting all of the confounding variables, influenza, and CHD data, and clean minds with which to judge the evidence.

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The authors reply
Os autores respondem

Maria Inês Reinert Azambuja & Bruce B. Duncan

Capturing determinants of vulnerability from modifications in disease occurrence

"*In science, just as in art and in life, only that which is true to culture is true to nature*" (Luwdick Fleck, 1979:35).

"*Once we recognize that state of the art is a social product, we are freer to look critically at the agenda of our science, its conceptual framework, and accepted methodologies, and to make conscious research choices*" (Richard Levins & Richard Lewontin, 1987, *apud* Krieger, 2001:668).

First of all, we wish to thank *Cadernos de Saúde Pública/Reports in Public Health* (CSP) for the opportunity to publish this paper. It presents a nearly 10-year-old hypothesis (Reinert-Azambuja, 1994) of an association between the 1918 influenza pandemic and the rise and fall in CHD mortality registered in the 20th century, which, prior to its submission to the CSP, had found no room in scientific journals.

During this period, we witnessed the emergence of inflammation as the best synthesis of accumulated knowledge about the morphological and biochemical characteristics of atherosclerotic plaques (Ross, 1993) and a substitution of inflammation for degeneration as the main pathogenic process leading to several additional common chronic diseases (Lorber, 1996).

Transitions in paradigms have implications for epidemiology (Pearce, 1996; Silva, 1990). As we know, the degenerative paradigm did more than target lifestyle-related exposures as potential risk factors for CHD. It also coherently targeted the individual as the most adequate observation unit for studying those exposures and their effects. For epidemiological research, this meant a huge investment in individual-centered epidemiological studies and a proportional abandonment of traditional, more society-oriented approaches to the understanding of causes of disease occurrence in populations (Pearce, 1996; Silva, 1990; Susser & Bresnahan, 2001). This trend now appears to be changing: "*epidemiology is in transition from a science that identifies risk factors for disease to one that analyzes the systems that generate patterns of disease in populations*" (Koopman, 1996:630).

We believe that the Editors' sensitivity towards a growing debate on the adequacy of current epidemiological methods and objects of study (Barata, 1997; Koopman, 1996; Kriegger, 2001; Levins & Lopez, 1999; Pearce, 1996; Susser & Bresnahan, 2001; Susser & Susser, 1996; Weed, 2001) has contributed to their allocation of this space in the CSP for the publication and discussion of our paper. We wish to thank Drs. Rosely Sichieri, Marcelo Urbano Ferreira, Guilherme Werneck, and Euclides Castilho & Nelson Gouveia for reviewing and commenting on our work. We hope that our reply to these critiques might be read as once instructed by Bacon, "*...not to contradict, nor to believe, but to weigh and consider*" (1597, *apud*, Miettinen, 2001:592).

To answer some of the doubts and objections they have raised, we would begin by taking a step back and emphasizing two points that are central to the discussion but – given the still dominant role of individual-centered epidemiologic reasoning – may have remained partially misunderstood.

The first point is that the hypothesis set forth in our paper refers to an association between two occurrences. We do not expect this association to immediately translate to the individual level. We never stated that influenza infection "caused" the individual cases of CHD recorded in the United States. What we said was that the influenza pandemic of 1918 (and the frequent smaller influenza epidemics following it until 1957) might have been responsible for the emergence (and shape) of the CHD epidemic curve observed during the 20th century. Such a difference may appear senseless at first sight. However, we must remember what was once said by Reuel Stallones (1980) and Geophrey Rose (1985): causes of cases are not necessarily the same as causes of case distributions in the population.

A case is an entity, an epidemic is a process. To understand the emergence and development of an epidemic one must focus on *variations*. Such variations in occurrence depend not only on correlated variations in "*exposures*" to specific "risk factors" for individual cases, but also, and perhaps principally, on variation in the proportion of "*vulnerable*" *exposed* individuals in the population, meaning a qualitative modification in the denominator of the occurrence equation according to time, person, and place.

Ecological studies attempt to answer not what caused disease in individuals nor even what caused a given rate of disease in a specific population, but raise plausible hypotheses as to what caused *differences* in rates over time, or across geographic areas. Differences in rates may be modeled as resulting both from relative differences in population exposures and relative differences in the average population vulnerability to those exposures. This vulnerability occurs at the individual level and might be considered an individual "risk factor" if its pathophysiological mechanisms were better understood and we had the means to measure its value in individuals. Until such conditions are met it can only be captured as it expresses itself, as a relative variation in disease rates over time or among populations, independently of variation in other known environmental exposures.

The hypothesis set forth in our paper might be read as follows: the H1N1 influenza "priming" was responsible for the emergence and distribution of differential acquired vulnerability to CHD among the US population; the total burden of the CHD epidemic was the result of the interaction between that differential vulnerability and other CHD-related environmental exposures (other infections, Western-style diet, smoking...) over time.

As we do not believe that the individual level of analysis is the most appropriate to explore the cause of the CHD epidemic and have made no attempt to directly infer CHD causation in individuals from an association between two distributions detected at the population level, we understand, as do other authors (Pearce, 1996; Szklo & Nieto, 2000) that objections based on the ecological fallacy do not apply to this case.

The second point is that according to the hypothesis, the 1918 influenza pandemic (and small influenza epidemics following it until 1957), and still more specifically, its effect on particularly vulnerable (young, white, male) members of the population, "*initiated*" the CHD epidemic which emerged in 1925 and begun to remit in the late 1960s.

This is completely different from saying, as do several individual-centered epidemiological studies, that infection may have a role as "precipitator" of acute myocardial infarction or CHD death. Again, the hypothesis refers to the cause of the epidemic. Of course, according to current biological knowledge, if the proposed association is true, reinfection of an individual "*initiated*" by influenza virus, or even by another infectious agent sharing cross-reacting antigens with it (Wucherpfennig & Strominger, 1995), among other factors, might "*precipitate*" MI or CHD death. But what we wish to emphasize is a possible role of infection in the emergence (and shape) of the CHD epidemic phenomenon.

Having discussed these two points, and, we expect, adequately answered comments related to them, we will attempt to answer the specific comments of each author.

Rosely Sichieri suggested the possibility of confounding by other variables like socioeconomic status (SES) and smoking. The association between SES and CHD mortality appears to have varied over time. Apparently, during the rise in CHD mortality there was an association between CHD and high SES. During the decline, CHD was found mostly among low SES groups (Wing, 1988). Infectious disease occurrence is highly related to SES. However, SES differences are probably less relevant during major epidemics. From 25 to 40% of the American population became recognizably ill during the pandemic. Serological surveys in the 1960s showed seroprevalences of anti-Hsw antibodies (reactive to pandemic-related strains of influenza virus) equal to or greater than 80% in cohorts born between 1888 and 1919 (Dowdle, 1999). More interestingly, as we mentioned, severe effects of influenza infection in 1918-1919 appear to have occurred mostly among the healthiest people in the nation, as evidenced by high mortality and morbidity among highly selected American soldiers (Crosby, 1989). One would expect the effect of SES on vulnerability to influenza infection to be greater after the peak in the pandemic, which could at least partially explain a similar transition in vulnerability to CHD to lower SES groups among later birth cohorts. Cohorts born after 1900 would hypothetically have been "primed" by influenza viruses during the smaller epidemics occurring from 1920-1957, after they had reached their twenties, the age at which, if this hypothesis is correct, the greatest priming would occur.

The fact that cardiovascular mortality trends in Minnesota from 1960 to 1978 (Gillum et al., 1984) were not explained by concurrent influenza epidemics cannot be taken as an argument against our paper's hypothesis. What we contended was that CHD mortality trends observed during and after the 1960s were probably dependent on the evolution of influenza epidemics occurring *several decades before* (when "priming" to future CHD development would have occurred). On the other hand, the increase in CHD mortality *rates* during the 1967-1968 influenza epidemic is evident in Figure 4 of Gillum's paper (and could be due to immune-inflammatory flares occurring in influenza-"primed" individuals upon reinfection).

Regarding smoking, the only way to consider it a confounder of the association we propose is attributing to this recent habit the still unexplained age (sex and race) distribution of morbidity/mortality seen during the 1918-1919 influenza pandemic – considered in our paper as a "proxy" for the distribution of CHD "priming" on influenza infection – or at least to show that the distribution of smoking among cohorts is correlated with this age/sex/race distribution. That would be an interesting possibility. Tobacco use greatly increased at the end of the nineteenth century, following the invention of the cigarette-rolling machine (1884) and the rise of mass consumer marketing (Proctor, 2001). Virtually an entire generation of men returned from World War I addicted to cigarettes (Proctor, 2001). However, very few women smoked at the turn of the century, because smoking was seen as immoral and a sign of bad character (Herrera, 1999). Until the late 1920s, tobacco companies feared advertising for women. More widespread cigarette smoking by women did not occur until the 1930s (Herrera, 1999). Since the age pattern of pandemic-related influenza deaths was not restricted to men, we could not attribute it to smoking. But if cigarette smoking was probably not the most important determinant of young adult morbidity and case-fatality in 1918-1919, the WWI addicted were mostly from the same birth cohorts of men who, we propose, were "primed" to CHD during the pandemic. Smoking by women, on the other hand, attained significance only in cohorts born after 1910, when the effects of influenza "priming" were fading. Smoking might thus explain the increasing sex ratios observed in CHD mortality over time, as influenza "primed" birth-cohorts (1880-1915) grew older.

Marcelo Ferreira highlighted the paper by Bainton et al. (1978) as the first to associate the excess cardiovascular deaths occurring during influenza epidemics with an influenza triggering of myocardial infarction. The suggestion of platelet aggregation by Bainton et al. (1978) (and of increased fibrinogen and factor VII levels by Woodhouse et al., 1994) as a link between respiratory (re?)-infection and myocardial infarction is probably part of the truth, either at a mechanistic level or as markers of an activated inflammatory process. But these acute phenomena cannot explain the continuing increase in the proportion of deaths attributed to organic heart diseases during successive influenza epidemics. As described in our paper, cardiovascular deaths increased from 1.6% in the 1918 pandemic (Collins, 1932) to 51% in 1957-1960 (Eickoff et al., 1961), accompanying the 1880-1915 birth cohorts in their trajectory towards the middle third of the 20th century.

As recalled by Ferreira, the resumption of interest in the infectious hypothesis for CHD occurred in the wake of the identification of *Chlamydia pneumoniae*, reported in 1986 (Grayston et al., 1986). Initial reports of a possible association between chronic *Chlamydia* infection and CHD were published in 1988-1989 (Richer, 1989; Saikku et al., 1988). But it was not until the late 1990s, when the inflammatory paradigm became predominant in the pathophysiological explanation of atherogenesis, that infection was seriously considered as a possible cause of CHD. In 1998, for the first time two seminars were devoted to this issue, one in Europe and the other in the United States. However, expectations regarding the definitive implication of *Chlamydia pneumoniae* (or any other infectious agent) in atherogenesis have yet to be fulfilled. More rigorous designs apparently weakened the seroepidemiological links between *Chlamydia* infection and atherosclerosis (O'Connor et al., 2001). Nonetheless, considerable evidence exists to support the hypothesis that infection may be involved in atherosclerotic disease (O'Connor et al., 2001). At present, the specific effects of antibiotic treatment remain unclear, and results of prospective randomized clinical trials are awaited, but they are not expected to provide convincing evidence for a causal relationship between *Chlamydia* infection and atherosclerosis (O'Connor et al., 2001). This difficulty in establishing an infectious etiology has resulted in two current trends in relation to the role of infection in atherosclerosis: (1) the attribution of a pathogenic role not to one specific infectious agent, but to the infectious burden to which individuals are exposed during their lives (Espinoloa-Klein et al., 2002) and (2) the categorization of infection as merely an additional risk factor, to be integrated into the multifactorial framework of CHD causation (O'Connor et al., 2001).

The first trend does not contradict the hypothesis presented in our paper. In the case of multiple sclerosis (Wucherpfennig & Strominger, 1995) several common pathogens (particularly from the herpesvirus, influenza, and papillomavirus families) were shown to share similar epitopes with the myelin basic protein, and each could independently initiate an autoimmune process leading to the disease. The possibility of several agents "initiating" the same condition was also advocated by Evans (1980) in discussing causes of cancer. According to both authors, this would explain why it is so hard to link the immunopathogenesis of a disease to a specific agent. Agreeing with them, we contend that an epidemic would be required to achieve that goal with respect to CHD. And none was so huge as the 1998 influenza pandemic. This is not to say that the H1N1 influenza virus would be the only infectious agent eventually associated with CHD initiation and/or progression. However, by the nature of the pandemic related to it, it may have been the agent best suited for disclosure through an ecological methodology.

As for the second trend – the consideration of infection merely as an additional risk factor to be incorporated into multivariate CHD causation models – such a stance risks missing those determinants that, as discussed above, could be suggested only upon variation in disease rates detected by population-level studies.

Agreeing with Ferreira, it would be very interesting to monitor CHD incidence among those affected by H1N1 viruses after they reappeared in 1977. Russia, a country recently experiencing dramatically increasing CHD mortality rates (Notzon et al., 1998), underwent a documented 14-year period (1977-1991) of epidemic H1N1 influenza virus activity (Kiselev et al., 1994). Yet we must be cautious. As we attempted to show in the our paper, what correlates well with the observed rise in CHD mortality is not the plain occurrence of H1N1 infection, but instead the occurrence of a severe response to infection, more common in young, white, male segments of the population, and which remains unexplained to date.

Guilherme Werneck's two observations about the evidence presented in favor of a correlation between the relative mortality associated with the influenza pandemic and the distribution of CHD deaths in the period 1920-1985 are accurate.

The first is that inclusion of CHD mortality data registered after 1985 in the figure would make the birth cohort decline less sharp (besides making the correlation during the CHD decline worse). True. Of course it would be convenient if the cohort distribution of 1918-1919 influenza and pneumonia mortality alone could predict the CHD mortality curve. In fact, it "explains" the most impressive feature of the curve: the change in direction of CHD mortality trends which occurs between cohorts born before and after the turn of the 20th century. However, in addition to the point-source exposure represented by the pandemic, to explain the right tail of the cohort distribution of CHD deaths requires incorporation of the effect of an extended period of lower levels of exposure affecting cohorts born after 1900, an exposure attributed to H1N1 epidemics following the

huge 1918-1919 pandemic until 1957. "Priming" by those epidemics is not taken into account in the figure.

The influenza and pneumonia total death toll due to influenza epidemics occurring during the inter-pandemic period (1920-1957) practically equaled the number attributed to the pandemic (611,000 X 675,000) (Glezen, 1996). However, the characteristic age distribution of influenza and pneumonia morbidity/mortality seen during the pandemic gradually faded out over this period in morbidity (Collins, 1944) and apparently disappeared in mortality (Glezen, 1996). Parameters for estimating *the cohort distribution* of influenza "priming" during those epidemics were poor. As the main impact of influenza moved west and into rural areas, the US influenza mortality surveillance system was not as well prepared to follow its trail. Influenza mortality data were collected in 95 American cities. From those, 31 were west of the Mississippi River and only 13 were west of the one-hundredth meridian, which cuts through the Dakotas, Nebraska, Kansas, Oklahoma, and Texas. Rural populations were not represented in the system (Collins, 1930). Age variation in influenza-related excess deaths occurring in those regions would remain undetected. Given these difficulties and uncertainties, we did not attempt to include such effects in the figure. If we had, we would have expected a closer correlation between both trends, even with a less sharp decline in CHD mortality resulting from the inclusion of more recent CHD mortality data.

The second observation is that the increase in mortality among younger people from more recent cohorts does not seem to return to some "original" baseline expected for those not exposed to the burden of H1N1 influenza. This is true. But as we have mentioned previously, we are not saying that H1N1 influenza infection, or the immune response to it, directly caused all the CHD cases registered since 1920.

Regarding the low value attributed by Werneck and Castilho & Gouveia to the correlation coefficient obtained for the association between longer persistence of H1N1 influenza and delayed onset of decline in CHD death rates, based on both the relatively small number of units of observation (nine) and on what they see as extreme values, we disagree. The observations refer to population-based data, involving huge numbers of deaths (10-year periods) and individuals at risk, making them more precise estimates of the true values. The observed correlation is corroborated by descriptive data reported in our paper regarding the geographic evolution of both occurrences. Its value is high, and we would expect it to be even higher if the surveillance system had captured the occurrence of flu-related deaths in small cities from the central and western regions and from rural areas of the country.

Castilho & Gouveia questioned the use of the "influenza and pneumonia" category for representing deaths attributed to influenza. They believe that 99% of those deaths would be due to pneumonia not clearly associated with influenza infection. This is a valid concern. But we wish to clarify that we used only secondary influenza and pneumonia mortality data (excess death rates) reported by the US Public Health Service as occurring during sharply defined increases in mortality from acute respiratory disease (Collins, 1930), a criterion which greatly increases their association with influenza infection.

We interpreted the distribution of pandemic-related deaths as the tip of a hidden iceberg of morbidity with similar age, sex, and racial distribution (see Figure 1 of our original article). From the figure we see that case fatality (deaths/diseased) in adulthood was less than 0.5%. Thus, in our understanding, CHD would be expected to develop precisely in the same age, sex, and racial group, and not in some complementary group of women, blacks, or the like.

We disagree with the low value attributed by Castilho & Gouveia to the attempt to integrate evidence obtained at the population level with that obtained at the clinical and biomolecular levels. Current trends in scientific research emphasize the need for theories based on multiple levels of information instead of the black box approach (Krieger, 2001; Susser & Bresnahan, 2001).

The hypothesis presented in our paper is a good example of the importance of ecological studies, the proper choice for studying causal determinants of *changes in occurrences*. The role of studies which attempt to capture group-level variations and their possible causes is currently being rehabilitated, and rightly so (Susser & Bresnahan, 2001; Szklo & Nieto, 2000). What is needed now are new modeling designs capable of hierarchically integrating knowledge generated at different levels (population, individual, sub-individual) of organization (Barbosa et al., 2000; Koopman et al., 2001; Krieger, 2001; Susser & Susser, 1996).

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