Similarities in mortality patterns from influenza in the first half of the 20th century and the rise and fall of ischemic heart disease in the United States: a new hypothesis concerning the coronary heart disease epidemic

Semelhanças entre o padrão de mortalidade por influenza na primeira metade do século XX e o padrão de mortalidade por doença isquêmica do coração no transcorrer do século, nos Estados Unidos: uma nova hipótese para a epidemia de cardiopatia isquêmica

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Abstract *The classic risk factors for developing coronary heart disease (CHD) explain less than 50% of the decrease in mortality observed since 1950. The transition currently under way, from the degenerative to the infectious-inflammatory paradigm, requires a new causal interpretation of temporal trends. The following is an ecological study based on data from the United States showing that in men and women an association between the age distribution of mortality due to influenza and pneumonia (I&P) associated with the influenza pandemic in 1918-1919 in the 10-49-year age bracket and the distribution of CHD mortality from 1920 to 1985 in survivors from the corresponding birth cohorts. It further shows a significant negative correlation (r = -0.68, p = 0.042) between excess mortality from I&P accumulated in epidemics from 1931 to 1940 (used as indicator for persistent circulation of H1N1 virus combined with vulnerability to infection) and the order of the beginning in the decline in CHD mortality in nine geographic divisions in the United States. In light of current biological knowledge, the data suggest that the 1918 influenza pandemic and the subsequent epidemics up to 1957 might have played a determinant role in the epidemic of CHD mortality registered in the 20th century.*
Key words *Mortality; Myocardial Ischemia; Influenza; Pneumonia*

Resumo *Os fatores de risco clássicos para o desenvolvimento de doença isquêmica do coração (DIC) explicam menos de 50% da queda na mortalidade observada desde 1950. A transição em curso, do paradigma degenerativo para o inflamatório/infeccioso, requer nova interpretação causal das tendências temporais. Este é um estudo ecológico, baseado em dados dos Estados Unidos, que mostra, em homens e mulheres, uma associação entre a distribuição etária da mortalidade por influenza e pneumonia (I&P) associada à pandemia de influenza de 1918-1919 na faixa dos 10 aos 49 anos e a distribuição da mortalidade por DIC, entre 1920 e 1985, em sobreviventes das coortes de nascimento correspondentes. Mostra ainda uma correlação negativa significativa (r = -0,68, p = 0,042) entre o excesso de mortalidade por I&P acumulado em epidemias entre 1931-1940 (utilizado como indicador da persistência da circulação de vírus H1N1 aliada à vulnerabilidade à infecção) e a ordem do início do declínio na mortalidade por DIC, em nove divisões geográficas dos Estados Unidos. Os dados sugerem, à luz do conhecimento biológico atual, que a pandemia de influenza de 1918 e as que se seguiram até 1957, pudesse ter tido papel determinante na epidemia de mortalidade por DIC registrada no século XX.*
Palavras-chave *Mortalidade; Isquemia Miocárdica; Influenza; Pneumonia*

In the course of the last 70 years, a rise and fall in mortality from coronary heart disease (CHD) occurred in several countries. In the United States, angina emerged as a significant cause of death in the mid-1920s (Stallones, 1980). From then on, CHD mortality rose steadily until the early 1960s, when it leveled off at around 35% of overall mortality (Havlick & Feinleib, 1979). The decline began in 1968 and accelerated after 1972 (Levi, 1981), resulting in a fall of more than 40% in CHD death rates in the last 30 years (Sytkowski et al., 1996).

The CHD mortality time trend has still not been explained satisfactorily (Metha et al., 1998), with traditional risk factors accounting for less than 50% of the variation in rates registered since 1950 (Sytkowski et al., 1996). As stated by Mizgala & Shulzer (2000), the results of the MONICA study and the disappointing results of primary intervention trials based on those risk factors suggest that "*it is perhaps time to recognize the possibility that trends in CHD mortality seen across the world in the past 30 years or so, may be driven by forces independent of the classic risk factors*" (Ebrahim & Davey-Smith, 1999, *apud* Mizgala & Shulzer, 2000:430).

Since the late 1970s, evidence provided by experimental and clinical studies (Koenig et al., 1999; Kol & Libby, 1999; Lindberg et al., 1992; Ridker et al., 1997; Ross, 1999; Schmitz et al., 1998) has challenged the traditional notion of CHD as a degenerative condition, supporting instead an alternative view of CHD as an immune inflammatory disease (Metha et al., 1998; Schmitz et al., 1998; Watanabe et al., 1996). Several authors have also postulated a role for infection in initiation and/or progression of CHD and risk of myocardial infarction or death (Hajjar et al., 1986; Kol & Libby, 1999; Nieto, 1998; Zhu et al., 2001). However, thus far few attempts have been made (Anestad et al., 1997; Mozar et al., 1990) to incorporate the infectious-inflammatory hypothesis into explanations for 20th-century CHD mortality trends.

The degenerative paradigm has attempted to explain the CHD epidemic as secondary to time-trend variation in *exposures* to risk factors for development of disease. An infectious-inflammatory hypothesis would support a somewhat different explanation, that is, one based more on a variation in *individual susceptibility* to CHD over time.

It has been shown that certain infections affect an individual's response to subsequent infections (Griffin, 1994) as well as to other environmental challenges (Evans & Brachman, 1986), among them being high-fat diets (Hajjar et al., 1986). Thus, theoretically, a massive occurrence of an infectious disease could have led to the emergence of the CHD epidemic, even if other environmental exposures (e.g.: high fat intake, smoking) had not changed over time, by modifying individuals' susceptibility to their effects.

A major worldwide infectious event immediately preceding the rise in CHD mortality was the 1918 influenza pandemic. Twenty-five percent of the US population (at least 25 million people) had overt flu during that pandemic, resulting in at least 500,000 excess influenza and pneumonia deaths (Crosby, 1989). Worldwide, the minimum estimated mortality was 21 million people, with the real number easily reaching 30 to 40 million (Crosby, 1989).

Influenza viruses circulating from 1918 to 1957 maintained an important overlap in terms of serological and biochemical laboratory tests, ecology, and public health effects, and are now all classified in the H1N1 subtype of influenza A viruses (Dowdle, 1999). Could the pathogenetic burden of H1N1 influenza infection on the US population explain the observed epidemiological pattern in 20th-century CHD mortality?

## H1N1 influenza in the United States

The Spanish flu of 1918 had unique characteristics compared to the 1958 (H2N2 sub-type) and 1968 (H3N2 sub-type) influenza pandemics (Crosby, 1989; Dowdle, 1999): (1) unusually high morbidity and mortality; (2) high male/female and white/black morbidity and mortality ratios; and, oddly, (3) highest morbidity and mortality burden among young adults.

As shown in Figure 1 (Collins, 1930; Crosby, 1989; US Bureau of the Census, 1955), the incidence of respiratory illnesses (with at least one day in bed) peaked in both sexes at age 10, followed by a drop in the twenties, a second peak during the thirties, and a significant fall in the forties. However, one-third to one-half of deaths were concentrated in the second and third decades of life. The consensus of the American Public Health Conference of December 1918 was that the most frequent victims of flu were "*those who had been in the best of physical condition and freest from previous disease*" (Crosby, 1989: 216). According to expert opinion, death was due not to direct viral damage but to the strength of the immune-inflammatory response to infection, greater in robust young (white, male) adults (Crosby, 1989).

We thus hypothesize that whatever immune-inflammatory mechanism caused a sex and age mortality pattern in 1918-1919 which differed from that of incidence of respiratory symptoms

1918-1919 Influenza and pneumonia morbidity and mortality (/1,000) by sex and age. US Registration States.
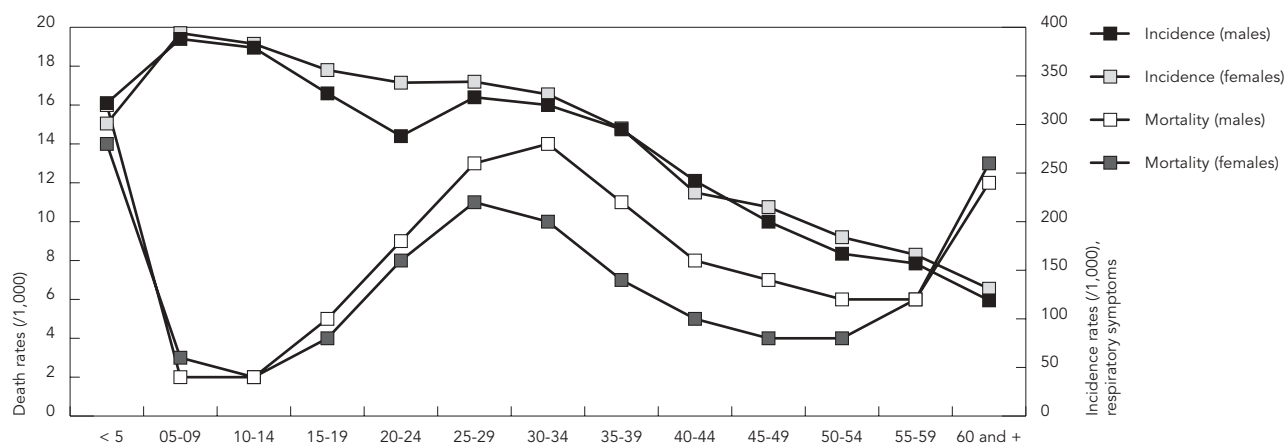
Source: Collins (1930); Crosby (1989); US Bureau of the Census (1955).

during the pandemic (see Figure 1) also "primed" survivors in a similar fashion, predisposing them to future development of CHD. If that were the case, then the relative distribution of influenza-related deaths among individuals ages 15 to 49 in 1918-1919 (a proxy for the distribution of some particular kind of immune-inflammatory response to infection across the range of exposed birth cohorts) should predict the occurrence of CHD mortality in survivors from the corresponding birth cohorts (from about 1870 to 1915) in the subsequent years. (The higher 1918-1919 influenza and pneumonia mortality at the extremes of life is presumably related to other mechanisms, irrelevant to the hypothesis discussed here, as influenza epidemics usually present greater mortality at the extremes of life.)

While flu activity showed a continuing decline from 1918 to 1957, such a trend was not uniform across the United States (Collins, 1930; Gover, 1943). Thus we further hypothesize that the reported geographic variation in time of onset of the decline in CHD death rates depended on the varying persistence of H1N1 viruses across the United States, and, through their effect, on a lower level but continuing CHD "initiation" taking place in later birth cohorts.

Methodology

This paper presents ecological associations between influenza and CHD occurrences across birth cohorts and across geographic areas of the United States, in support of the two hypotheses presented above.

Birth cohort correlation

United States gender- and age-specific mortality data were used to graphically compare the burden of the 1918-1919 influenza pandemic with that of the 1920-1985 CHD epidemic across birth cohorts.

Influenza data

Sex and age strata-specific influenza mortality rates were calculated using the number of deaths from influenza and pneumonia in 1918 (Crosby, 1989) and an estimate of the population residing in the US Registration Area for 1917 (US Bureau of the Census, 1955) used at that time for national tabulations of vital events and covering approximately 80% of the US continental population (Collins, 1930). Deaths occurring during 1918 and 1919 were assigned to January 1, 1919. They were then adjusted to reflect the age the deceased would have had in 1920, so that the age-specific rates could be plotted for birth cohorts according to the usual center of 10-year birth cohort intervals (July 1 of years ending with 0 or 5). Since one and a half years elapsed between January 1, 1919, and July 1, 1920, this adjustment was performed for each age stratum, adding, in weight-

ed fashion, the 1918-1919 influenza and pneumonia stratum-specific death coefficient of the age stratum in question (weight = 0.85) to the death coefficient of the next youngest stratum (weight = 0.15).

CHD mortality data

For the most recent period, 1960-1985, CHD mortality rates were calculated based on gender- and age-specific data (number of deaths and population) referent to the total US population (all races), obtained from the Division of Vital Statistics of the National Center for Health Statistics (NCHS, 1990). Age-specific CHD mortality was defined as the number of deaths classified according to the International Classification of Diseases (ICD) revision effective in the year of death, divided by total population in the same year, in each 10-year stratum. ICD versions prior to 1950 were too variable in their definitions of heart disease to characterize, in a standardized way, the US CHD death trends (Coulson, 1975). Thus, to document birth-cohort trends during the ascendant limb of the CHD epidemic curve, we used published tables on the number of deaths ascribed to coronary heart disease (and population), by age and sex, referent to Seattle-King County (State of Washington) only (Ravenholdt, 1966). In this subset of data, the assigned cause of death resulted from a review and tabulation of all death certificates registered in that area from 1920-1960, at every fifth year, in accordance with the 1955 international standards (ICD-7). Using both sets of data, we tabulated CHD mortality according to 10-year age and birth cohort strata. To make the total CHD mortality burden comparable across different distributions of age in successive birth cohorts, we defined, separately for men and women, a referent birth cohort having a mid-period number of survivors at each successive 10-year age interval (from ages 40-49 to 80+) equal to the number of individuals at the respective 10-year age strata of the 1940 US total population (US Bureau of the Census, 1954). We then estimated age strata-specific standardized numbers of CHD deaths for successive birth cohorts by multiplying the age stratum-specific death rate corresponding to each specific birth cohort by the number of individuals estimated at mid-period in the respective 10 year age stratum in this standard population. Next, we calculated the total period age strata-specific standardized numbers of deaths, multiplying this mid-period number of deaths by 10. In doing so, we extrapolate a one-year mortality experience to that of a 10-year period of observation of the cohort members as they pass through the specified 10-year age interval. Finally, we graphically summed the age strata-specific standardized numbers of deaths within each birth cohort in order to obtain a standardized estimate of the total CHD mortality burden for each 10-year birth cohort.

Geographic correlation

We used the Spearman correlation coefficient to quantify the association, across the US geographic divisions, between longer persistence of H1N1 influenza viruses, estimated by total excess death rate from influenza and pneumonia measured during the whole of each epidemic occurring from 1931-1940 (Gover, 1943) and delayed onset of decline in CHD death rates estimated by the proportion of Metropolitan State Economic Areas in which the decline in CHD mortality had already begun in 1968, as analyzed by Wing et al. (1986).

Results

Birth-cohort trends

Figure 2 graphically compares the relative mortality associated with the 1918-1919 pandemic with that from the CHD epidemic in the period 1920-1985 across successive birth cohorts, separately for men and women. The solid line connects points representing the distribution of mortality from influenza and pneumonia in 1918-1919 for birth cohorts roughly corresponding to those with 10-50 years of age in 1918-1919 (see Figure 1). The vertical bars display the standardized number of CHD deaths, shaded to represent deaths in different age strata, among those same birth cohorts. As can be seen, for both sexes, for cohorts born in the last third of the nineteenth century, as pandemic-related mortality increases so does the observed CHD mortality. Both distributions attain their peak in cohorts born just before 1900 and then begin to fall towards the latter-born cohorts. In cohorts born successively after 1900, a growing excess of observed CHD mortality in relation to that expected, in relative terms, from the pandemic mortality curve, can be seen, with this excess being somewhat larger for men.

Geographic variability in onset of CHD decline

As can be seen in Figure 3, after 1930, H1N1 influenza-related excess deaths varied consider-

Figure 2

Relative distributions of 1918-1919 influenza and pneumonia death rates (line) and of 1920-1985 CHD standardized[a] number of deaths by age (bars) in successive birth cohorts, according to age and sex, United States.

US men

US women
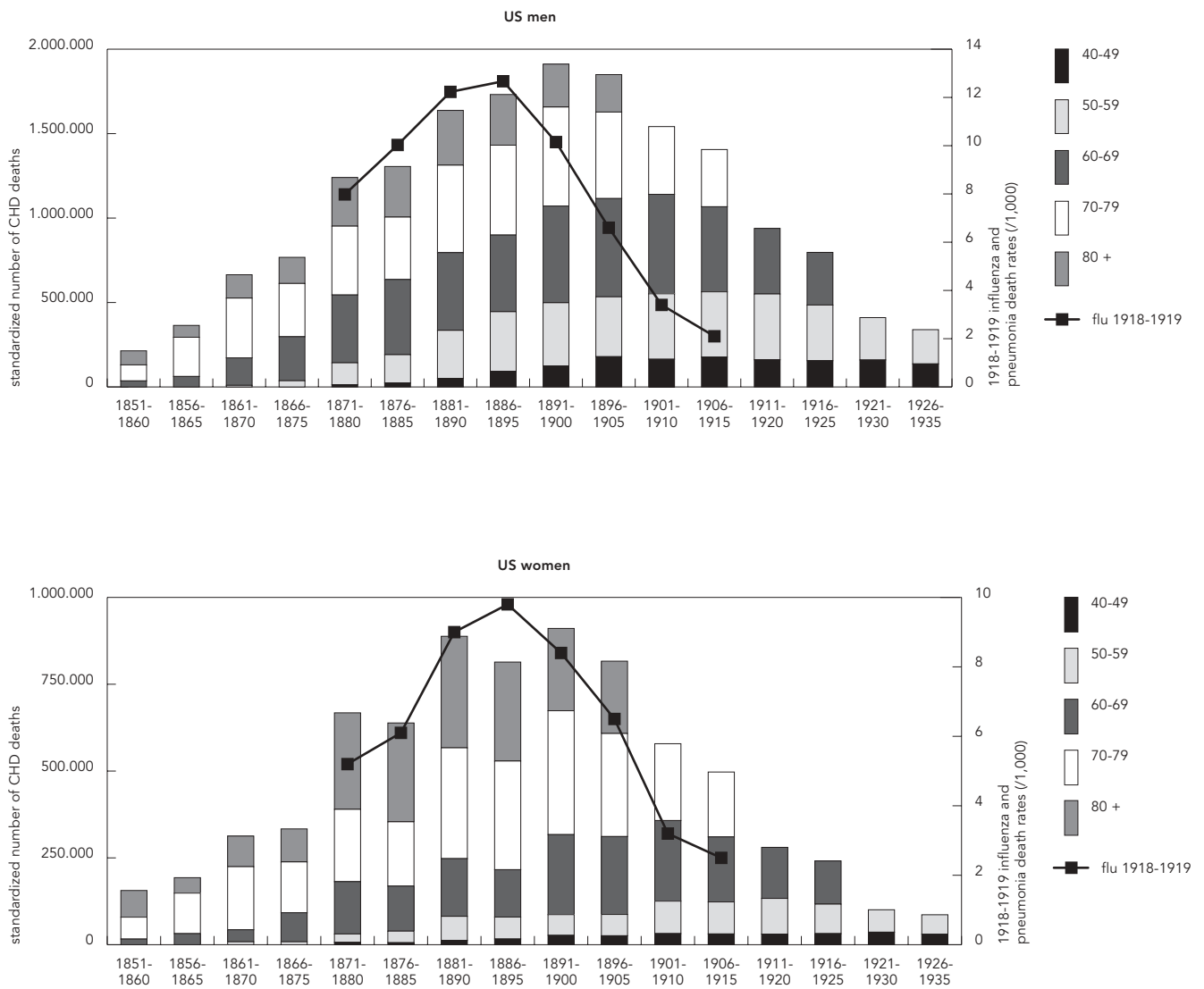
Sources: CHD mortality data from *National Center for Health Statistics, Vital Statistics of the United States, Vol. II, Mortality. Published and Unpublished Data – Selected Years* and US Bureau of the Census (1954). Influenza data from Crosby (1989) and US Bureau of the Census (1955).
[a] Standard population: 1940 US population, by sex and age strata.

ably across the US Geographic Divisions, being less in the Northeast, Mid-Atlantic, East North Central, South Atlantic, and Pacific Divisions compared to the West North Central, East South Central, West South Central, and Mountain Divisions. The onset of decline in CHD mortality also varied considerably, having begun in 100% of the Northeast and 98.5% of the Pacific Metropolitan State Economic Areas in 1968, but in only approximately 60% of Metropolitan Areas of the West North Central and East South Central Divisions.

A notable negative correlation exists between excess influenza and pneumonia mortality after 1930 and early decline in CHD mortality across the United States (r_s = -0.68; p = 0.042).

Figure 3

Correlation[a] between persistence of H1 influenza activity after 1930 (measured by 1931-1940 influenza excess death rates – Gover, 1943) and timing of the onset of the decline in CHD mortality (measured by proportion of metropolitan SEA[b] with declining CHD death rates in 1968 and earlier, Wing et al., 1992) across the US Geographic Divisions[c].
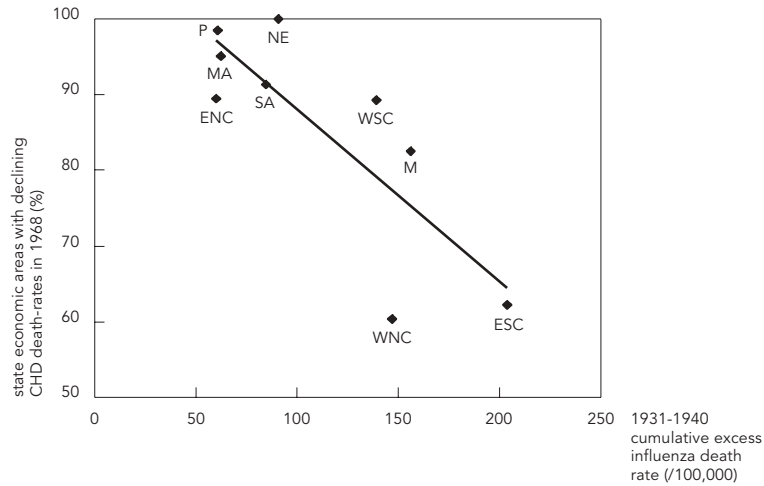
[a] Spearman (rs) correlation.
[b] SEA = State Economic Areas
[c] NE = Northeast; P = Pacific; MA = Mid-Atlantic; ENC = East North Central;
SA = South Atlantic; WSC = West South Central; M = Mountain;
WNC = West North Central; ESC = East South Central.

Discussion

The above data demonstrate two epidemiologically important ecological associations between the burden of H1N1 influenza infection on the US population in the early 20th century and the mid-century rise in CHD mortality. Age-related influenza and pneumonia mortality during the 1918-1919 pandemic predicts well, separately in men and women, the relative distribution of CHD mortality across the corresponding birth cohorts. The burden of H1N1 influenza activity post-1930, measured by influenza and pneumonia death rates, showed a strong association with delayed declines in CHD mortality across US Geographic Divisions. In fact, it might help explain the observed persistence of CHD mortality across the latest-born cohorts beyond that expected on the basis of an estimate which considered the 1918-1919 pandemic alone (see Figure 2).

Additionally, there are important socio-demographic similarities between those most affected by the 1918-1919 influenza and those who died from CHD. CHD mortality was always higher in men than women (Stallones, 1980). Male/female death ratios during the pandemic also varied from 1.2 at ages 10-19 to 1.7 at ages 40-49 (Crosby, 1989) (see Figure 1). CHD mortality was higher in whites than in blacks from the mid-1920s until about 1963, when a crossover in death rates occurred (Gillium, 1982). As mentioned, one of the unique characteristics of the 1918 pandemic was its unexpectedly high white/black mortality ratio. Not only was mortality from influenza and pneumonia lower in blacks but, during the pandemic, "*death-rates for all causes of blacks between 25 and 45 years of age were below those of their white counterparts, probably for the only time in the history of the nation*" (Crosby, 1989:229).

As flu epidemics disappeared from the Northeast and Pacific regions and influenza mortality decreased and became more localized in the Mountain and Southern regions of the country, (1) specific demographic characteristics of those populations (on average with a higher proportion of blacks compared to the Northeast and Pacific), (2) higher variability in rates of exposure (due to lower levels of circulating virus), and (3) differential susceptibility to H1N1 infection across social strata (as demonstrated by Sydenstriker, 1931) could explain the Eastern/Southern (Stallones, 1980), white/black (Gillium, 1982), and socioeconomic (Wing et al., 1992) crossovers in CHD mortality rates registered during the decline. The decline and more recent leveling off (Rosamond et al., 1998) in CHD incidence is consistent with progressive exhaustion of the influenza-priming effect within the surviving population.

Thus, these epidemiological findings support our hypothesis that gender, race, age, and geographic differentials in the burden of pathogenic effects due to H1N1 influenza infection in the US population could help explain the main epidemiological characteristics (gender, race, birth cohort, and geographic pattern) of the 20th century CHD mortality epidemic.

Speculations on pathogenic mechanisms involved in an influenza/CHD mortality association

Epidemiological clues

The proportion of excess deaths occurring during influenza epidemics attributed to organic heart diseases grew considerably during the ascending phase of the CHD epidemic, from 1.6% in 1918-1919 to 18.4% in the minor epidemics occurring during 1920-1929 (Collins,

1932), and to 51% (cardiovascular-renal causes) of a total of 86,000 excess deaths registered during the 1957-1960 Asian influenza epidemics (Eickoff et al., 1961).

Beginning in the 1960s, a continuing improvement in survivorship, reflecting mostly a declining recurrence of myocardial infarction subsequent to initial diagnosis, was documented (Elveback, 1979). Although improved survivorship has usually been attributed to improved medical care, a change in disease/host relationship over time has been considered a possibility (McKinley et al., 1989). As first suggested by Gordon & Thom (1975), the reduction in death rates from CHD could be partially attributable to the continuing decline in influenza activity and the absence of extensive influenza epidemics after 1968. If the hypothesis proposed here is correct, reduction in repeat exposure of H1N1 "primed" individuals to subsequent influenza infections might have been the determining factor in the change in disease-host relationship regarding CHD progression and death.

It is worth noting that historical records indicate the possible occurrence of a previous rise and fall in CHD mortality in Britain over the last third of the eighteenth century (Azambuja, 1995). Heberden's original description of the anginal syndrome in 1772, a time when its cardiac origin had not yet been established, followed a period of significant influenza activity in Britain, with epidemics recorded in 1727, 1732, 1737, and 1760 (Crosby, 1989).

Clinical/pathological clues

Sudden death was a hallmark of the CHD epidemic, especially during its ascending phase. According to McKinlay et al. (1989), at the height of the CHD epidemic, almost two-thirds of CHD deaths were sudden and unexpected and occurred outside hospitals, mostly as a result of acute arrhythmias. During the decline, this component of CHD mortality fell more dramatically than did incidence of acute myocardial infarction or long-term post-MI mortality (McKinlay et al., 1989). Sudden death was also a common component of cardiovascular deaths in influenza epidemics (Oseasohn et al., 1959), and it has recently been shown that influenza vaccination confers protection against sudden death (Siscovick et al., 2000). Obstruction of arteries supplying the conduction system of the heart (first septal artery, sinus node artery, atrioventricular node artery, posterior descending artery) is a preponderant finding among patients with sudden cardiac death,

compared to apparently healthy subjects dying of accidental causes (Velican et al., 1989).

During the 1918 influenza pandemic, the most frequently observed circulatory disturbance was bradycardia. Particularly during convalescence, bradycardia often became marked. A small group of patients showed arrhythmias with either atrial or ventricular extrasystoles and conduction disorders, varying from simple prolonged P-R interval to bradycardia with "escaped sino-nodal beats", partial block (1:2, 1:3; 1:4), and complete heart block. Such effects on the heart were transitory and non-responsive to atropine. At autopsy, some dilatation of the right side was commonly observed, with diffuse changes such as "cloudy swelling", evidence of "parenchymal degeneration", loss of striation, but usually no clear-cut inflammatory changes of the myocardium (Anonymous, 1958). Endothelial cells were not described. However, infection and inflammation of arteries supplying the conduction system of the heart could explain both arrhythmias during the 1918 pandemic and sudden CHD deaths occurring during decades of relatively high influenza activity. Cytomegalovirus and influenza virus are capable of modulating the in vitro production of IL-6 by human endothelial cells (Visseren et al., 1999). And the highly pathogenic avian influenza virus A/FPV/Rostock/34 (H7N1) was shown to be highly endotheliotropic (Feldman et al., 2000).

Biomolecular clues

Infection by one strain of influenza A virus focuses the antibody (and possibly the T-cell) (Klenerman & Zinkernagel, 1998) response to infections by different subsequent strains of influenza viruses on epitopes shared by the original hemagglutinin antigens, a process known as "original antigenic sin" (Dowdle, 1999; Hennessy & Davenport, 1958). Similar to reactivation of rheumatic heart disease upon reinfection by group A beta-hemolytic streptococcus (Guilherme et al., 2001) and exacerbations of multiple sclerosis following viral-like infections (Fujinami, 2001), immune responses elicited at each new encounter with an influenza virus could reactivate inflammatory pathways to CHD, originally established by a first encounter with a H1N1 influenza virus and some specific immune response to it. In this regard, atherosclerotic lesions are mostly located in areas which would logically receive the highest loads of both viruses and immunoinflammatory products from the infected lungs: the left side of the heart, the coronary arteries, and the aortic arch with its main branches.

Besides a reinfection-driven autoimmune reactivation of endothelial inflammation leading to acute CHD events and/or chronic progression of vascular disease, another possibility must also be considered: that flu infection or the immune response to it interfered with lipid metabolism, leading to increased susceptibility to high serum cholesterol levels. Pleskov et al. (1994) described, in some strains of influenza viruses, a significant mimicry of the amino acid sequences involved in cell attachment of the viral hemagglutinin with those of apolipoprotein B involved in LDL binding to high-affinity LDL receptors. Upon reinfection, co-localization of anti-apo B antibodies at sites of viral penetration in the vascular bed could result in intimal LDL accumulation followed by oxidation and subsequent foam cell formation (Steinberg & Witzum, 1990).

Though speculative, a mechanism involving cross-reactivity between the H1N1 influenza strains and apoB-LDL or the LDL receptor could be a link from infection to hypercholesterolemia and CHD mortality and shed new light on the "diet-heart" controversy (Blackburn & Jacobs, 1984). Within populations, the effect of dietary fat/cholesterol intake on serum cholesterol levels might depend more on the efficiency of LDL uptake, the latter possibly influenced by a cross-reactive immune response to a previous H1N1 influenza infection.

In short, although biological links between influenza and CHD remain to be proven, intriguing leads do exist.

Conclusions and final remarks

Ecological studies are weak designs to establish causality. However, the strength and consistency of the several different ecological correlates shown here, coupled with a potential biological plausibility of this epidemiologically-driven hypothesis within an immune-inflammatory paradigm of atherosclerosis, do make the associations presented worthy of further consideration.

Current evidence demonstrates that the diet-heart paradigm, which gave support to most of the research and intervention policies related to CHD during the 20th century, cannot adequately explain all the features related to the CHD time trends (Kuulasmaa et al., 2000; Metha et al., 1998; Mizgala & Shulzer, 2000; Taubes, 2001). Since the 1990s, several other diseases traditionally associated with degeneration were shown to have, instead, an inflammatory basis and an infectious etiology (Lorber, 1996). Inflammation has also become the main paradigm of CHD pathogenesis, since Ross & Glomset (1976a; 1976b) first demonstrated its dominant role in atherogenesis (Ross, 1999). We hope that this study, which expands previously presented (Reinert-Azambuja, 1994) evidence for the influenza/CHD epidemic hypothesis, will stimulate further investigation of influenza's role in the 20th-century course of CHD, permitting extension of the inflammatory paradigm and introduction of the infectious hypothesis to the interpretation of the rise and fall in CHD mortality, a worldwide occurrence described by the WHO (1969, *apud* Gordon & Kannel: 1617) as "*the greatest epidemic mankind has faced*".

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