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INFLUENZA RECYCLING AND SECULAR TRENDS IN MORTALITY AND NATALITY[1]

By Maria Inês Reinert Azambuja

ABSTRACT

Secular variations in longevity and in population aging are of huge interest to actuaries. It is shown here that temporal changes in mortality and natality accompany the recycling of influenza A viruses, i.e., the re-exposure of human populations, from time to time, to influenza A viruses antigenically similar to viruses (H1, H2, H3) that circulated in the past. Mortality (and natality) change as birth cohorts (whole population and maternal) with specific types and levels of vulnerability to influenza A re-infections, acquired through early-life effects of infection with one (period-specific) influenza A sub-type, course through subsequent influenza A environments over time. Epidemiologic evidence of association between secular trends in mortality (and natality) and interactions between birth-cohort and period effects of influenza A circulation is presented both for the U.K. and the U.S. New interpretations to several epidemiologic and demographic observations follow from this finding.

KEYWORDS

Longevity; Mortality; Natality; Influenza; Epidemiology; Demography

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1. Introduction

"*Read not to contradict, nor to believe, but to weigh and consider.*"

— Bacon, 1597

The main ideas developed in this paper were first presented on October 21, in a multidisciplinary conference called "Joining Forces in Mortality and Longevity" (2009). The theme was "Drivers for Change" and my contribution would be to discuss possible factors driving mortality patterns by year of

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birth, an issue regarded as of great relevance by members of the actuarial profession (Willets, 2004; Richards *et al*., 2006). The word "Change", within this context, refers to the remarkable gain in life expectancy associated mainly with the unexpected global decline in coronary heart disease (CHD) mortality registered over the last 30 years (Centers for Disease Control and Prevention, 1999; Unal *et al*., 2004). In spite of several attempts to understand its determinants, they remain elusive. An explanation would be that they cannot be identified because they lay outside the realm of our still dominant degenerative paradigm.[2]

1.1 *From Degeneration to Infection-Inflammation and Early Life Determinants of Disease Occurrences*

During the last two decades, several movements have concurred to change the way we model disease causation. Among them, we can mention:

(1) pleas for the substitution of inflammation for degeneration regarding the physiopatogenics of chronic diseases (Ross, 1993; Libby *et al*., 2002; Azambuja, 2004; Ridker, 2007; Azambuja, 2008);
(2) demonstrations of an early-life circumstances role in the development of chronic diseases (Lucas, 1991; Barker, 2001; McMillen & Robinson, 2005; Gluckman & Hanson, 2006; Victora *et al*., 2008);
(3) emphasis on vulnerability besides exposures (Levins & Lopez, 1999; Azambuja, 2004; Azambuja & Levins, 2007; Knauth, 2008);
(4) rediscovery of old studies of cohort trends in disease occurrences and early-life determination of population longevity (Derrick, 1927; Kermack *et al*., 1934; Davey-Smith & Lynch, 2004; Richards *et al*., 2006; Richards, 2008); and
(5) attempts to integrate all these subjects — early-life experiences, inflammatory phenotypes, acquired vulnerability and cohort trends in diseases mortality — in an unified theory (Azambuja, 2004; Finch & Crimmins, 2004). This paper follows this track.

Built upon concepts already used to explain the rise and fall in coronary heart disease (CHD) mortality in the U.S. (Reinert-Azambuja, 1994; Azambuja & Duncan, 2002; Azambuja & Duncan, 2002a; Azambuja, 2008), a new paradigm is proposed, capable of explaining the variations

[2] It is the scientific paradigm — *the basic assumptions that rule our theories of science* — that defines (1) *what* is to be observed and scrutinized; (2) the kind of *questions* that are supposed to be asked and probed for answers in relation to this subject; (3) *how* these questions are to be structured; and (4) *how* the results of scientific investigations should be interpreted.(Kuhn, 1996; Fleck, 1935).

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in secular trends of disease occurrences and projecting their future developments.

1.2 *Influenza and the Rise and Fall in CHD Mortality: Cause and Effect?*

In 1994 this author showed that a cohort association existed between the 20th century rise in CHD mortality and the 1918 Influenza Pandemic excess-mortality. In the U.S., both events disproportionately affected cohorts born before the turn of the 20th century (Reinert-Azambuja, 1994; Azambuja & Duncan, 2002). A complex hypothesis was developed during the following years to explain this observation, involving the concepts of original antigenic sin, recycling of influenza A viruses and cross-reactive auto-immune responses to hetero-subtypic influenza re-infections (Azambuja & Levins, 2007; Azambuja, 2008; Azambuja, 2009b). These concepts and an updated version of the Influenza-CHD hypothesis are briefly summarized below.

The *original antigenic sin* is a phenomenon recognized since 1953 (Francis *et al*., 1953) and described by Davenport *et al*. (1969) as follows: "the major antigens of the [influenza] strains of first infection of childhood permanently orient the antibody-forming mechanisms so that, on subsequent exposures to influenza viruses, the cohort of the population would respond with marked reinforcement of the primary antibody" (p453). This mechanism would explain, for example, the resistance shown by very old individuals against the 1969 H3 Pandemic (Simonsen *et al*., 2004), and now, of individuals older than 60 years of age against severe effects of the 2009 pandemic (Azambuja, 2009b). Their antibody forming mechanisms were prepared to promptly react and produce antibodies against those viruses, because they were similar to the ones associated with their first influenza experience.

The *influenza A recycling* is the re-introduction in the population, from time to time, of subtypes of the influenza A viruses antigenically similar to viruses that circulated in the past. The antibody spectrum of the human population acts as a limiting influence on the spread of strains antigenically alike their recent predecessors. On the other hand, the possibilities of viable variations in influenza A antigens seem to be limited. Together, these conditions favour the recycling of old influenza strains (Davenport *et al*., 1969; Dowdle, 1999). The chronology of circulation of influenza A sub-types is still in dispute, but the transition periods are usually described as follows (Centers for Disease Control and Prevention (CDC), 1996; Kilbourne, 2006; Doshi, 2008):

1957 — transition from H1 to H2;
1968 — transition from H2 to H3;
1976-77 — re-introduction of H1 strains and its co-circulation with H3 strains until at least 2009.

Viruses associated with the 1957 (H2) and the 1968 (H3) pandemics are examples of recycling of antigens prevalent at the end of the 19th century and

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at or about the turn of the 20th century (Davenport *et al*., 1969; Masurel, 1969; Dowdle, 1999). According to Dowdle (1999), the H3 subtype that emerged in 1968 recycled antigens from the 1890 Pandemic virus, but there is no consensus about the time of H3 circulation in the 19th century (Davenport *et al*., 1969; Masurel, 1969; Simonsen *et al*., 2004).[3]

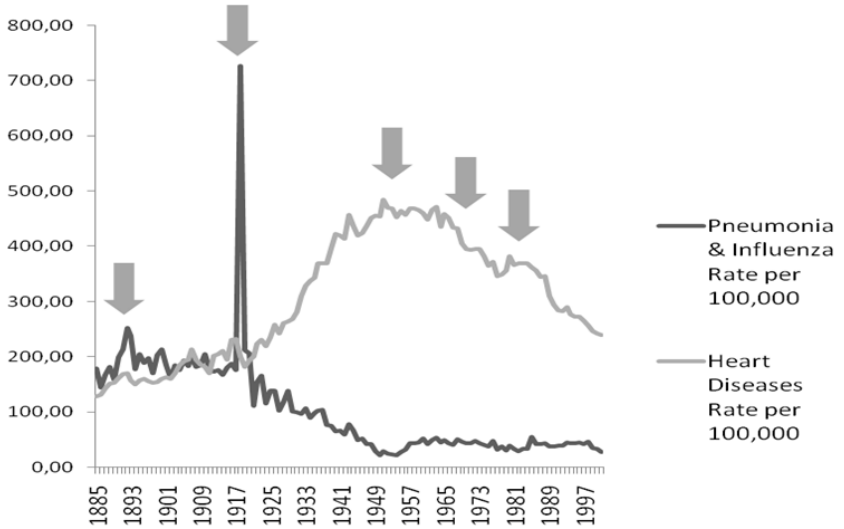
Hetero-subtypic immune responses are immune responses that are engendered by the current infection but based on viral antigens shared by the current and the priming influenza viruses (as an effect of the original antigenic sin). Since these responses are not tailored specifically to combat the current infection, they not only may be inefficient, but they may initiate immuno-pathogenic inflammatory reactions and diseases as well (Chen *et al*., 2003; Thomas *et al*., 2007).

Based on these new set of infectious/immuno-inflammatory references, an explanation of the rise and fall in CHD mortality, alternative to the one supported by the degenerative paradigm, is summarized in the following paragraph.

Individuals originally primed by the H3 influenza virus subtype, belonging to cohorts born at the end of the 19th and the beginning of the 20th century, showed increased vulnerability to die upon re-infections by H1 (circulating until 1957) and H2 (until 1968) influenza subtypes. Hetero-subtypic immune responses may explain the severe acute respiratory syndrome that occurred during the 1918-19 H1 Pandemic (Joris *et al*., 2003), as well as all the features associated with the mid-20th century CHD cases (hypercholesterolemia, lipid infiltration) and deaths (inflammation and thrombosis) (Azambuja, 2008). The beginning of the decline in CHD mortality among H3 primed birth-cohorts coincides with the re-introduction of H3 viruses in 1968. Furthermore, the re-introduction of the H1 subtype in 1976 and its relatively more intense co-circulation with H3 viruses during the early 1980s coincide with a delay in the ongoing decline in CHD mortality in the U.S. (see Figure 1 and also Azambuja, 2009a).

Thus, the association between influenza and CHD proposed here is complex. The increasingly recognized influenza triggering of CHD events

[3] The first isolation of a human Influenza A virus was in 1933. For epidemics occurring before that, the association with specific types/subtypes is presumptive, based on studies of anti-influenza antibodies to different influenza A sub-types in sera of large numbers of persons of different ages (Francis *et al*., 1953). There are disagreements and gaps in our knowledge (Davenport *et al*., 1969; Masurel, 1969; Masurel & Heitjink, 1983; Dowdle, 1999). Our current classification may also be insufficient to accommodate significant differences among strains classified within the same subtype today, like the H1 viruses associated with the 1943 and 1947 epidemics (Dowdle *et al*., 1969; Kilbourne, 2006). Additionally, recent phylogenetic analyzes show that all pandemic influenza strains of the 20th century were generated through a sequence of reassortment events occurring over some years before pandemic recognition (Smith *et al*., 2009).



Source: Massachusetts Department of Public Health, Registry of Vital Records and Statistics, April 26, 2004. The arrows indicate the 1890 (H3), 1918 (H1), 1957 (H2), 1968 (H3) and 1976 (H1-H3) transitions

Figure 1. Secular trends in heart diseases and pneumonia and influenza mortalities, Massachusetts 1885-2000

(Warren-Gash *et al*., 2009; Azambuja, 2010) would occur only when the "right" population constitution (one with H3 primed birth cohorts aged 40 years and more) crossed periods with high circulation of non-H3 strains, as it happened in the 1950s and 1960s and from 1976 to the mid-1980s (Azambuja, 2009a).

2. Generalization — Influenza and Secular Changes in Disease Occurrences and Longevity

The hypothesis presented in Section 1 suggests that effects secondary to a human-influenza co-adaptation may be associated with causes of disease cases (early life determination of immune-inflammatory phenotypes — original antigenic sin) and with causes of variations in disease occurrences (varying cohort patterns of acquired vulnerability — influenza recycling).

Historic evidence suggests that a previous CHD epidemic occurred towards the end of the 18th century, in Britain. The clinical syndrome

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described and called "Angina Pectoris" by Heberden in 1772, and firmly associated with hardening and narrowing of the coronary arteries before 1808, had practically disappeared in 1850, to re-emerge only at the beginning of the 20th century (Azambuja, 1995). These cycles of rise and fall in CHD mortality possibly constitute particular cases of a general effect emerging at the human-influenza interface. Different combinations of priming and re-infecting influenza strains would be expected to have other manifestations. The human-influenza interface must be further investigated, as it may be the origin of the historical variations in longevity, with temporal effects both in natality and in mortality.

2.1 *Influenza and the Developmental Origin of Diseases*

It has become a consensus that fetal and early postnatal development constitutes the most vulnerable period of human life, in regard to later adverse effects of environmental exposures (Lucas, 1991; Barker, 1998; Davey-Smith & Kuh, 2001; Drake & Walker, 2004; Barker *et al.*, 2005; Gluckman & Hanson, 2006; Lawlor, 2008; Victora *et al.*, 2008). The prenatal and early postnatal environment affect gene expression, and epigenetic changes may constitute an important mechanism of programming for later effects (Lucas, 1991; Drake & Walker, 2004; McMillen & Robinson, 2005). Metabolic disruptions associated with poor nutrition have been the main proposed pathway between early life environmental exposures and adult health or disease (Lucas, 1991; Barker, 2001; McMillen & Robinson, 2005; Victora *et al.*, 2008). Mechanisms associated with other environmental maternal exposures such as smoking, alcohol, and environmental toxins are under investigation (Davey-Smith, 2007). But the effects of early life infections on the future health of individuals and populations only now seem to be receiving due attention (McEniry *et al.*, 2008; Dowd *et al.*, 2009). Still, infections have been taken just as triggers to future diseases of children made particularly vulnerable to them by other early life determinants (like poor nutrition) (Dowd *et al.*, 2009).

Interestingly, during recent years, economists are the most active researchers on later life effects of intra-uterus infection. They see the 1918-19 influenza pandemic as a perfect natural experiment to explore differences in late-life effects across birth-cohorts with different intra-uterus rates of exposure to influenza (Mamelund, 2004; Almond & Mazumder, 2005; Snyder, 2007; Mazumder *et al.*, 2009). Almond & Mazumder (2005) report that cohorts that were *in uterus* during the pandemic exhibited an excess of impaired health outcomes in the 1980s relative to cohorts born a few months earlier or later. Mazumder *et al.* (2009) also compare cohorts at supposedly different levels of prenatal risk (born respectively in the first (Q1) and fourth (Q4) quarters of 1919) with respect to the prevalence of CVD after the age of 60 years. They found that, among men, occurrence of CVD was 25.6% among Q1 born and 20.8% among Q4 born individuals. The difference was

shown to be significant when expressed as excess-proportion (23.1%) of the relative difference (4.8%).

2.2 *Influenza and Natality*

The 1918-19 influenza had a very strong impact on natality, both due to maternal mortality and to fetal losses. In Norway, for example, it is estimated, based on data covering the period 1918-23, that 67 excess maternal deaths from all causes, or 18.3 deaths per 1,000 pregnant women, were caused by the Spanish influenza, and that 45 excess spontaneous abortions or 4.0 per 1,000 women 5-6 months pregnant, and 335 excess stillbirths or 22.1 per 1,000 women 7-9 months pregnant occurred due to the Spanish influenza (Mamelund, 2004). These calculations are probably underestimates, and omit abortions that occurred between conception and the fifth month of pregnancy (Mamelund, 2004). In the U.K., mortality of all women aged between 15 to 49 years during the 1918 pandemic was 4.9 per 1,000, but that of pregnant women was between 5.3 to 5.7 per 1,000 (Reid, 2005). Influenza infection precipitated fetal losses. Maternal mortality from miscarriages associated with the pandemic increased 10 times, from 0.16 per 1,000 in 1917 to 1.6 per 1,000 (one in 624 pregnancies). A great many more non-fatal spontaneous abortions possibly occurred (Reid, 2005). The second wave of the 1918 pandemic raised post-neonatal mortality well above its normal winter peak, some months after the peak (February, April and June 1919). The effect on stillbirths, on the contrary, was concentrated during the second wave. Reid concludes that influenza infection in the first and second trimesters of pregnancy can provoke premature delivery, and therefore still births or vulnerability to early death (Reid, 2005). Based on five influenza A epidemics which occurred in the U.K. in 1951, 1953, 1957, 1961, and 1970, Griffith (1972) shows elevated early neonatal mortality associated with all except the 1957 epidemic. The effect was most pronounced in infants born some months after the peak of the epidemics, and was associated with prematurity, which suggests some adverse effect operating intra-uterus. He also shows that birth weight by month of birth, based on 70,000 live births or about 8% of all live births in England, was found to be lower in the first quarter of 1969 compared with the corresponding period in 1970 in the seven areas studied, and in the second quarter in five of the seven areas. The author also refers to a paper by Doll *et al*. (1960) suggesting that influenza in pregnancy results in a tendency to low birth weight. Other authors have also reported correlations between month-of-birth, birth-weight and mean-age of death, suggesting association with seasonal differences in nutrition and infectious diseases (Doblhammer & Vaupel, 2001).

2.3 *Birth-Cohort Variations in Vulnerability*

As recently discussed by Davey-Smith & Lynch (2004), a striking characteristic of the huge decline in British mortality registered during the

19th and early 20th centuries is its strong cohort pattern, recognized by actuaries (Derrick, 1927; Davidson & Reid, 1927), medical scientists (Kermack *et al*., 1934) and demographers (Tutt, 1953), and periodically rediscovered. As reviewed by Davey-Smith & Kuh (2001), Derrick, in 1927, showed that mortality rates in any particular age depend on the year of birth, and showed that rates of death plotted against year of birth instead of year of death presented a remarkable parallel pattern. Kermack *et al*. (1934) expanded Derrick's analysis in a landmark paper that showed and discussed birth cohort influences on adult disease risk. Davey-Smith & Kuh (2001) calls them "*prescient''* by using their ecologic analyses to inform hypotheses regarding early-life exposures and their influence on later disease.

> "The figures behave as if the expectation of life was determined by the conditions which existed during the child earlier years. We may postulate that, constant hereditary endowment being assumed, the health of the child is determined by the environmental conditions existing during the years 0-15." Kermack *et al*. (1934, p680).

In 2004, Finch and Crimmins proposed that the birth-cohort pattern of mortality results from cohort morbidity phenotypes representing inflammatory processes that persist from early age into adult life. But they failed to identify the cause of the birth cohort phenotype variation. In the same year, Azambuja (2004, p854) published a paper anticipating the ideas discussed here:

> "Influenza viruses have co-evolved with human populations for centuries. Their encounters may have resulted in varying patterns of relative distribution of adaptive capabilities (selected genotypes and adapted phenotypes — e.g. immune profiles) of human populations to new environmental challenges, over time and across space. During the past decade, Influenza has been recognized as an ideal system for investigating ecologic and evolutionary issues. Mathematical modeling has been increasingly used to explore the evolutionary dynamics emerging from the adjustment between viral populations and immune phenotypes. It seems, however, that our culture of attributing disease to external agents has still "biased" those studies towards the understanding of the evolution of the virus. An alternative would be to use the influenza system to unravel the evolution of patterns of vulnerability in human populations."

2.4 *Period Effects on Secular Trends in Population Mortality*

In spite of the recognition of a persisting strong cohort pattern in the secular evolution of mortality (Finch & Crimmins, 2004; Willets, 2004; Richards *et al*., 2006), distortions identified in the cohort trends and the abrupt rise in longevity observed during the last decades seem to have weakened the primacy of cohort over period approaches to population forecasting (Tujapulkar & Boe, 1998; Barbi & Vaupel, 2005). Kermack *et al*. (1934) had already documented distortions on cohort declines in mortality introduced by period effects. As shown by Davey-Smith & Kuh (2001), the distortions increased after 1930.

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Associations between influenza epidemics and concurrent increases in mortality from all causes (and, in particular, other infectious diseases, pulmonary, cardio, cerebro and renovascular diseases, and diabetes) have been described for centuries (Creighton, 1891; Collins & Lehman, 1953; Langford, 2002; Reichert *et al.*, 2004). But, to this author's knowledge, influenza had never been considered, until now, as the cause of the distortions in the birth-cohort trends documented over time.

3. Hypothesis

It will be shown in this section that trends in mortality (and natality) result from interactions between birth-cohort and period effects, as birth cohorts with distinct patterns of vulnerability acquired as a result of early-life effects of influenza priming course through varying influenza environments over time. The trends would be expected to reflect the recycling of influenza viruses both as birth cohort and period effects. Thus, different outcomes would be expected, depending on combinations of the recycling effects upon the birth-cohorts (past) and the calendar years (present), as described in Table 1.

Mortality trends by age would increase, remain stable or decrease depending on effects of the influenza subtype circulating in the year of the death upon the birth-cohort specific inflammatory phenotype acquired through early life influenza priming. Based on the particular case of the Influenza-CHD association, one could expect that disagreement between priming and re-infecting subtypes increased mortality (or sustained it at higher levels) and agreement decreased mortality (or sustained it at lower levels).

Table 1. Possible short-time outcomes for the mortality trends resulting from combined birth-cohort and period effects of influenza recycling

Neighbour birth cohorts	Small period of successive calendar years	
	Same influenza re-exposure	Varying influenza re-exposures (corresponding to periods of current pandemics)
Same influenza priming	Stable trend (high, low)	Period effect
Varying influenza priming (corresponding to periods of past pandemics)	Cohort-effect	Combined effects — variations favouring disclosure of the effects

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3.1 *Method*

This is a descriptive study. It graphically presents U.K. and U.S. mortality and natality trends over the period 1933 to 2000, and temporally compares variation in numbers of live births and in numbers of young adults' deaths (taken as proxies for variations in occurrence of severe maternal influenza infection), considering the accepted periods of dominant circulation of specific influenza-A subtypes, namely:

1957 — transition from H1N1 to H2N2;
1968 — transition from H2N2 to H3N2;
1976-77 — re-introduction of the H1N1 subtype and its co-circulation with the H3N2 subtype until 2009.

In the U.S., co-circulation between H1N1 and H3N2 occurred until 1989 and after 1995-96 (Brammer *et al.*, 2000).

Mortality data for the U.S. and the U.K., and numbers of live births relative to the U.S. were obtained from the Human Mortality Database (2009). Numbers of life births in the U.K. were obtained from the U.K. Office of Health Statistics (National Health Statistics, 2009). Natality data is presented as numbers of live births for the U.S. and the U.K. according to calendar years. Mortality data are graphically presented by one-year intervals of age, calendar year and birth-cohort.

Death-coefficients versus numbers of deaths

The temporal evolution of the number of deaths was found to disclose better the birth-cohort or calendar-time variations for our purposes. Of course, when looking at numbers of deaths instead of death rates, we need to consider variation in the sizes of the respective birth cohorts. For this reason, estimates of the relative sizes of the birth cohorts (based on the cohort numbers of live-births) are displayed when indicated.

3.2 *Results*

3.2.1 *Secular trends in all-causes mortality in the U.S. and the U.K., from 1933-2000 — evidence for influenza period, cohort and combined effects*

Figures 2a to 2f display the mortality trends (all-causes) in the U.S. and the U.K. as death-coefficients (ages 40 to 90 years) by calendar years (Figures 2a, 2b), and numbers of deaths (ages 40-72 years) by calendar-years and corresponding birth-cohorts (Figures 2c to 2f).

The comparison of the mortality trends by one-year of age-interval in the U.S. and the U.K. is fascinating, both for their similarities and differences. Mortality maps of both countries show, in the years corresponding to the circulation of H1N1 strains (before 1957), strong vertical marks (**A**) corresponding to influenza epidemics occurring in 1935-36 and 1936-37 in the U.S. (Collins & Lehman, 1951), and in 1936-37, 1940 and 1950-51 in the

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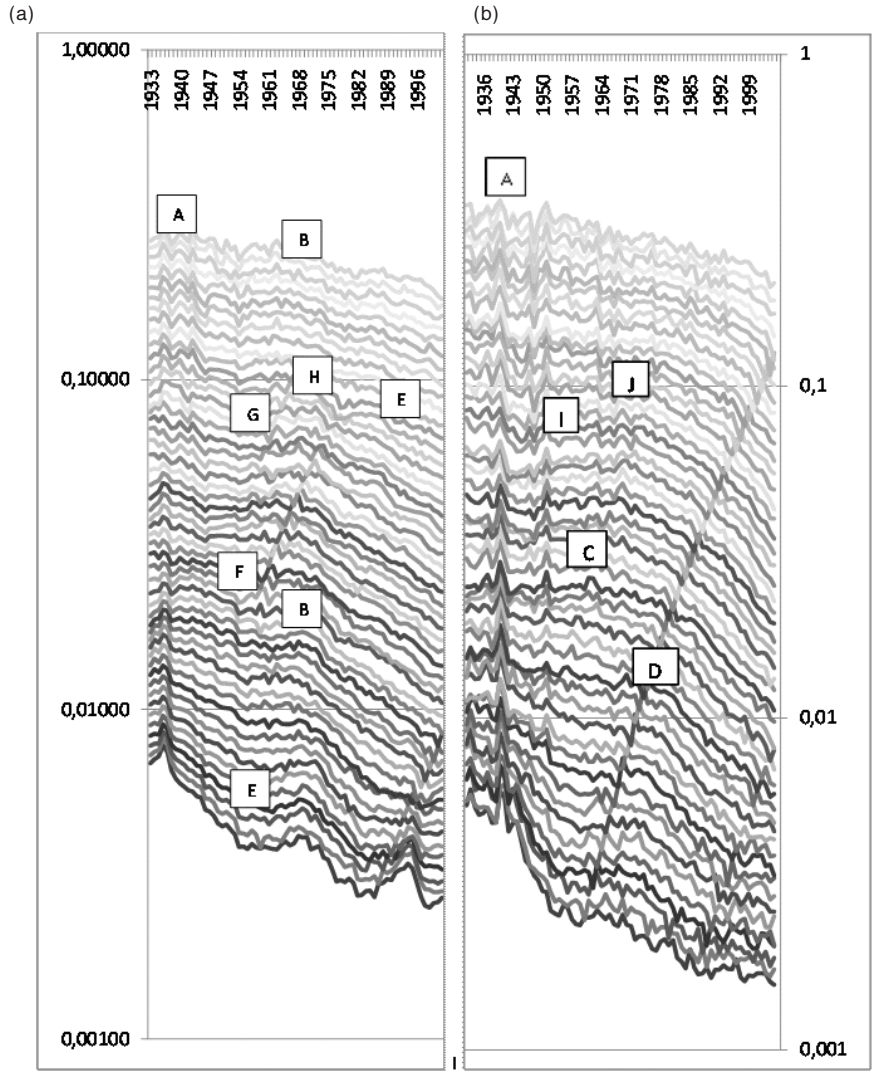

Figure 2a and b. Mortality trends (all causes) by 1 year of age intervals and calendar years. US (a) and UK (b) males, ages 40-90 years

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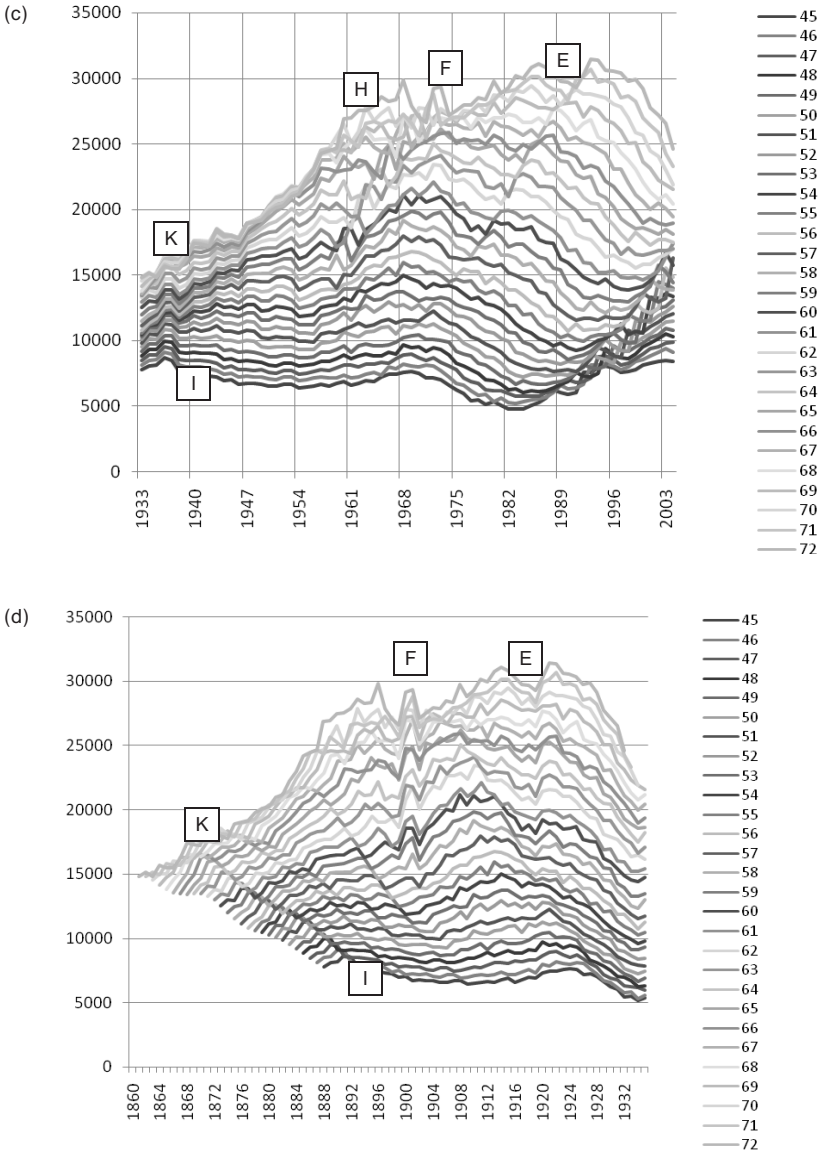

Figure 2c and d. Numbers of deaths (all causes) by 1 year of age-intervals according to calendar years (c) and birth-cohorts (d). US males, ages 45-72 years

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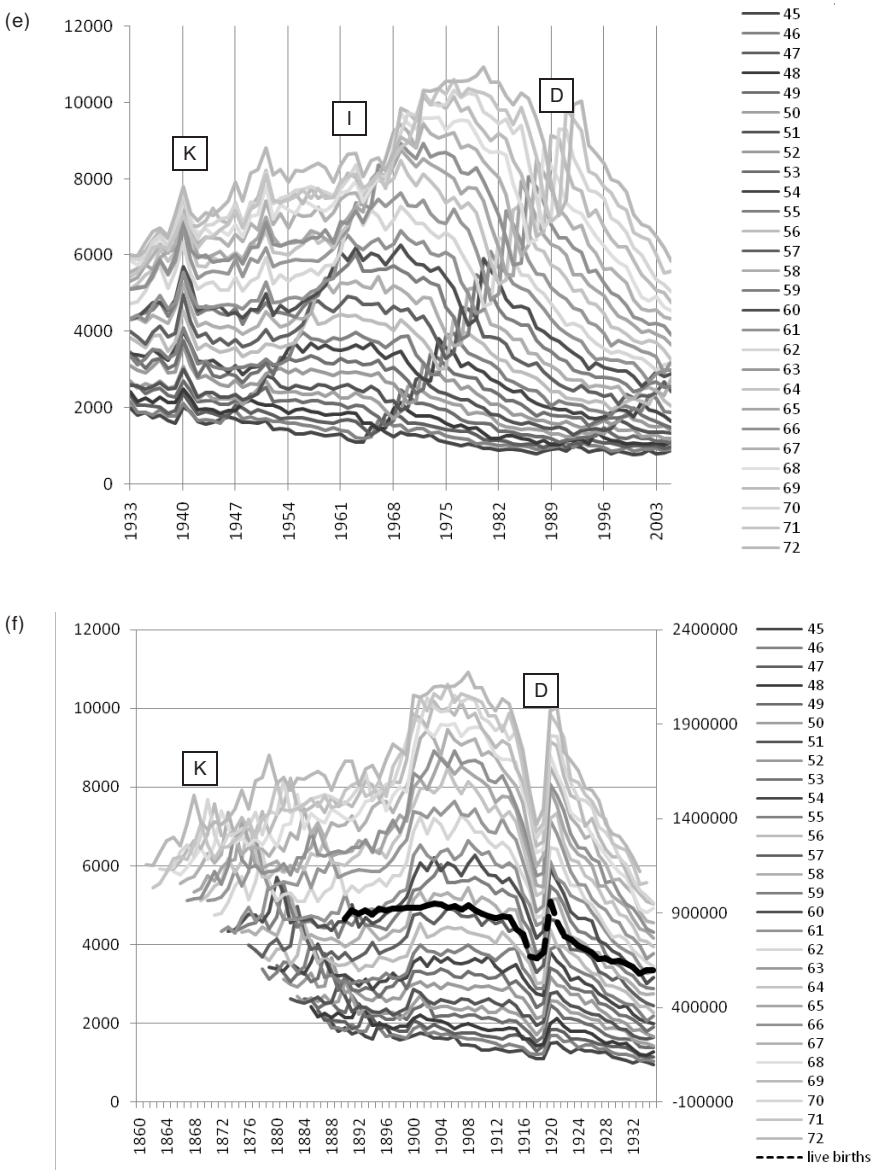

Figure 2e and f. Numbers of deaths (all causes) by 1 year of age-intervals according to calendar years (e) and birth-cohorts (f). UK males, ages 45-72 years

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U.K. (Stuart-Harris, 1953). The excess-mortality in years corresponding to H1N1 epidemics in the U.K. is greater than in the U.S. The 1951 pandemic, very significant in the U.K., has practically no effect upon the U.S. mortality experience.[4]

An equally strong vertical mark **(B)** corresponds, in the U.S., to the 1972-73 epidemics (H3 era) (Viboud *et al*., 2004)**.** The decline in mortality was already initiated after1968 in the U.S., but it is intensified after 1972-73 (according to this theory, due to increased number of re-infected with concordance between priming and re-infecting subtypes). In the U.K., a weak epidemic mark seems to exist in this same year, but it does not initiate a decline in mortality, which, in the U.K., seems to be better described not as a period effect as in the U.S., but as a cohort effect (**C**).

Besides the vertical marks corresponding to the mid-century epidemics (period effects), the mortality maps display intriguing transversal marks, some crossing periods of circulation of different influenza subtypes, like the ones seen in the U.K. (**C, D**), and others restricted to the period of circulation of a specific subtype, like the ones seen in the U.S. during the circulation of H2N2 strains **(E-G).**

The transversal marks **C** in the U.K. and **F** in the U.S. are birth-cohort marks corresponding to the transition to the 20th century, a period marked by significant mortality in both countries attributed to effects of recurrent influenza outbreaks encompassing the 1899-1900 pandemic (Potter, 2001).

The transversal mark **D** in the U.K. corresponds to the period 1915-20, which encompasses the 1918-19 pandemic (H1N1) and influenza outbreaks in 1915-16 and 1916-17 (H3?) in both countries, with elevated mortality among the aged (Olson *et al*., 2005).

The transversal mark **G** in the U.S. unveiled during the circulation of the H2N2 sub-type, corresponds to the 1890 Pandemic, supposedly associated with an H3 strain; and the weak transversal mark **E** in the U.S., partially unveiled during the H2N2 period and again during the co-circulation of the H1N1 and the H3N2 strains after 1975, corresponds to the 1916-20 period, and is much less striking than its U.K. counterpart.

While in the U.S. the increase in all-causes mortality that encompasses the rise in CHD mortality has an obvious period effect (from the early 1950s (H1 era) to the end of the H2 era in 1968-69) that visibly corresponds to the cohorts born from 1890-1900 **(H)**, in the U.K. the all-causes mortality rates seem to have attained and maintained higher levels since the 1951 epidemic **(I)**. The effects of the H2 circulation (from 1957 to 1968) were less significant

[4] According to Viboud *et al*. (2006), the 1951 epidemic was responsible for the largest increase in winter deaths from pneumonia and influenza and all-causes in the period 1950-99 in the U.K., with 1.3- to 1.4-fold higher crude excess death rates than those seen in 1957 (H2N2 pandemic) and in 1968 (H3N2 pandemic). In Liverpool, the 1951 influenza mortality far exceeded the deadliest of three 1918-19 influenza waves.

and apparently restricted to the cohorts born just before the turn of the 20th century **(J).**

In Figures 2c, 2d, 2e, 2f, secular trends in mortality in the U.S. and the U.K. are presented as numbers of deaths by age according to year of death (Figures 2c and 2e) and corresponding year of birth (Figures 2d and 2f). The period and cohort effects described before are more evident here. Period effects corresponding to some epidemic years — 1936-37 in the U.S., and 1936-37 and 1940 in the U.K. (**K**) — affect practically all ages (birth-cohorts), while in other cases, as in years corresponding to the 1962 epidemic in the U.K. and the 1940 epidemic in the U.S. (**L**), the effects seem to be confined to a limited range of birth cohorts (discordance between priming and re-exposure) sparing others (concordance between priming and re-exposure).

In the same way, the transversal marks reflect interactions between concurrent influenza exposures and birth-cohorts' priming. The strong transversal mark observed in the U.K. mortality map (Figures 2b, 2e and 2f) corresponding to those cohorts born between 1915-20 as they transverse the H2N2 (1957-68), H3N2 (1968-75) and the last H1N1 & H3N2 (1975-2009) periods, at a closer look, show a variation within that range of birth-cohorts as we follow their trajectory through periods with different dominant influenza subtypes. (The mark itself shows, in Figure 2b, as a more curvilinear pattern.) This suggests variation in birth cohort priming during the 1915-20 period, with varying cohort effects over time among that range of birth-cohorts, as they are exposed to different subtypes of influenza-A viruses after the 1950s.

Many other observations arising from a comparison between the trends in the two countries could be highlighted, but the point that we want to make here is that the evidence of association between secular trends in mortality and birth-cohort and period effects of influenza infections is overwhelming.

3.2.2 *Trends in natality in the U.S. and the U.K.*

Figure 3 shows the evolution in the annual number of live births in the U.S., from 1933 to 2007, and in the U.K., from 1860 to 2006. There are important differences among them, such as: (1) a huge reduction in the U.K. number of live births during WWI, and after 1920-21; and (2) a significant reduction in live births in the U.K. in 1940-41, and after 1946-47 until 1957, compared to the U.S.

There are also similarities among the trends in some periods, like the 1940s and after 1965. There are localised declines in numbers of live births observed in 1940-41 in the U.K., 1944 in the U.S., and after 1947 both in the U.K. and the U.S. After 1965, a relatively good (but not perfect) correlation exists between trends in the number of live births in the U.S. and U.K. As it is shown in Figure 3, the numbers of births decrease from 1965-77, increase, on the average, from approximately 1977 to 1990, decline

Sources: U.S.: Human Mortality Database
U.K.: http://www.statistics.gov.uk/statbase/ssdataset.asp?vlnk=9526&More=Y

Figure 3. Evolution of the total live births (thousands) in the U.S. and the

during the early 1990s, and are apparently increasing again since 1998 in the U.S., and 2003 in the U.K.

While the world wars possibly had a main role in the reduction of births shown in U.K. trends, influenza epidemics also had their share. Bradshaw *et al*. (2008) recently state that a distinction between the effects of war and those of influenza upon rises in tuberculosis is impossible in times of war. The same would apply to their effects upon declines in natality. An influenza epidemic occurred in the U.K. in 1940-41 that increased the number of deaths at practically all ages, but especially among cohorts born after 1900. According to Stuart-Harris (1953), owing to the war, this was the only epidemic not adequately documented in Great Britain. An increase in mortality also occurred in 1940 in the U.S., but it was smaller and restricted to cohorts born before 1900. Outbreaks of influenza A also occurred in November of 1943 in the U.K., U.S. and Canada (Stuart-Harris, 1953). The combined effects of the WW2 and influenza epidemics explain the

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disturbances in cohort trends of mortality described by Davey-Smith & Kuh in 2001.

War and epidemic-related mortality during the 1940s in the U.K. hit harder cohorts born during and soon after WWI, adding further losses (now of adults at reproductive ages) to cohorts smaller from birth as a result of the previous World War and the 1918 Pandemic. Thus, it seems that a birth-loss wave effect initiated with the WWI and the 1918 Influenza pandemic and further amplified by the WW2 (and concurrent influenza epidemics) had a huge impact on the future trend of live births and population growth in the U.K. It may still be contributing to the differences in live births' trends among the U.S. (ascending) and the U.K. (stabilized) registered during the last 30 years. The U.K. never regained, in a sustained way, the annual number of births that it had before 1915, which is one of the causes of the accelerated aging of its population.

3.2.3 *Effects of the influenza recycling upon natality in the U.S.*

To explore the possibility of a correlation between influenza recycling and natality in a long time-series, it would be better to use the U.S. data, because in the U.S. natality trend was less affected by losses associated to the world wars.

If influenza has an effect upon natality, increases in young-adults mortality should correspond to concurrent decreases in natality, and be in some way associated with changes in influenza circulation. Figure 4 shows the U.S. trend in numbers of live births and the concurrent trend in numbers of deaths between ages 19 to 29 years (shown as its inverse) for the period 1933 to 2004.

The correlation between natality and young adults' mortality is striking. And the main inflections in the time trend curves correspond to moments of influenza recycling. Young adults mortality declines and natality increases in the H1 era (until 1957 (1953-63)). Then, mortality increases and natality declines after 1958 until around 1978 (H2-H3 eras). Notice that the two interruptions in the rise in natality registered from 1940-57 (H1 era) immediately follow the 1943 and the 1947[5] H1 epidemics. After the 1947 epidemic, it was only in 1951 that the number of births reached again the levels of 1947, but the curve suggests that a deficit in natality may have persisted until 1954-56.

But an association between natality trends and circulating influenza subtypes, if it exists, is expected to be more complex. It is possible to see that, even within a small range of ages (ages 19 to 29 years) there are differences in mortality trends by age (birth-cohort) across the calendar years, and that

[5] An unusually large drift event in the hemagglutinin of A/H1N1 viruses was reported in 1947. There were no cross-protection to the 1947 virus by vaccines containing the 1943 H1N1 strain (Kilbourne, 2006).

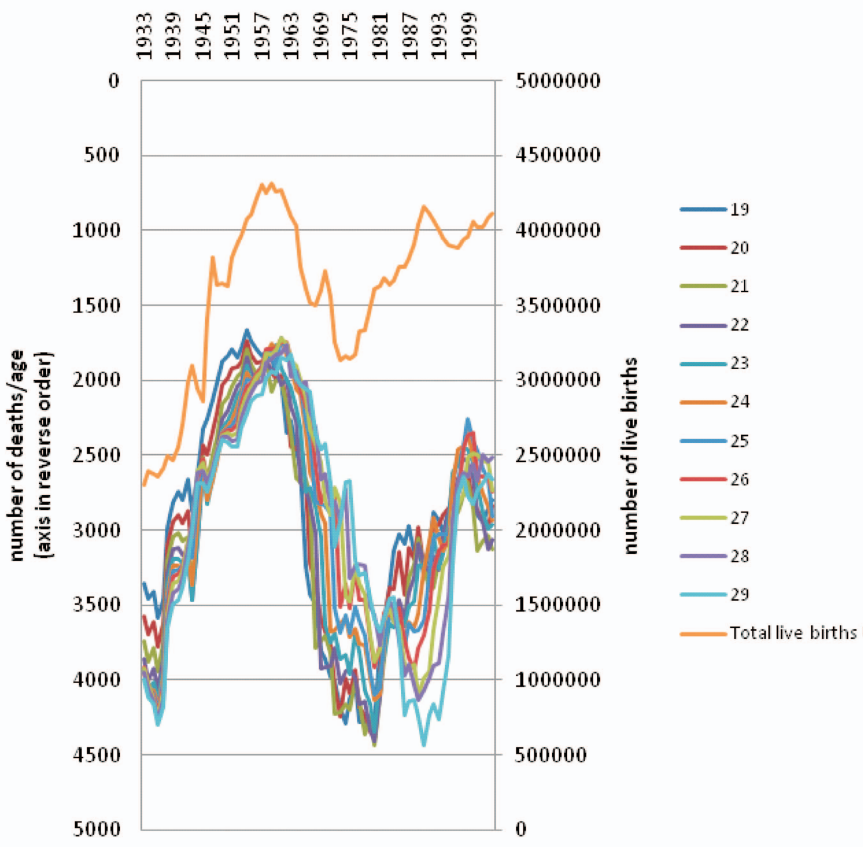

Figure 4. Trends in numbers of deaths at ages 19 to 29 years and concurrent number of live births, U.S., 1933 to 2004

the natality curve seems to represent a summary measure of those different age (cohort) trends. This is more evident after 1978 (re-emergence of the H1 subtype and its co-circulation with H3 strains).

According to this paper's general hypothesis, birth losses would depend on selective pressures posed to the fetuses by maternal influenza infections, given the mothers' particular early life experiences with similar or different influenza viruses. If both priming and re-infection, were associated with the same influenza subtype, the selective pressure would decrease and natality increase. Otherwise, natality would decrease. Thus, periods of increase in

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numbers of live births would suggest a growing sub-type concordance between viruses circulating at the time of maternal priming (birth cohort) and the time of maternal re-infection, and vice-versa.

For an average intergenerational time-interval estimate of 25-30 years (Tremblay & Vezina, 2000), and an H1 period of circulation of (supposedly) 49 years (1918-57), it would be expected that natality increased from 1933 until 1957, as the proportion of mothers primed and re-infected by H1 viruses increased. It would also be expected that natality decreased during the H2 and H3 eras, spanning the next 20 years (1957-68 and 1968-77), considering that most mothers during that period would have been primed by H1 viruses. The findings are in accordance with this.

The steep increase in mortality (shown as its inverse in Figure 4) and the decrease in natality seen after 1968 (H3 era) would correspond to maternal cohorts born from 1943-47, a period encompassing two important H1 epidemics (and significant H1 influenza priming). After 1977, co-circulation between H1 and H3 viruses occurred, but H1 viruses were more frequent before 1990 (see Table 2). Thus, mothers giving birth from 1977-90 were

Table 2. Influenza viruses circulating in the U.S., 1969-2008

Year	Influenza viruses	Year	Influenza viruses
1969	H3	1989	H1
1970	H3	1990	H1 B h3
1971	Mix, h3	1991	H3 B
1972	H3	1992	H3
1973	H3 e b	1993	Mix h3
1974	B e h3	1994	H3
1975	H3	1995	mix
1976	H3,h1	1996	H3, b
1977	h1,b h3	1997	h3
1978	h1,b,h3	1998	h3, B, (h1)
1979	H1 b	1999	H3,h1 (b)
1980	H3 B	2000	H1,B (h3)
1981	H3 B h1	2001	H3,b (h1)
1982	B h1	2002	b, H1,h3
1983	H3	2003	H3 (b)
1984	B h1	2004	H3, B
1985	H3 B h1	2005	H3, h1,b
1986	B h1	2006	H1,h3,B
1987	H1	2007	H3,H1, b
1988	H3	2008	H1,b (h3)

Sources: Simonsen *et al*., 2000:(1969-95); Lui *et al*., 1987: (76-77, 78-79); CDC/influenza:1996-2008. (underlined years had explicit mention to H1 viruses. Capital letters were used to indicate the more frequently identified strain, and parenthesis to represent small frequencies of recovery.

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born, on the average (less 25-30 years), from1947 to 1965, during H1 (1947-57) and H2 (1957-65) periods. The decline in young adults mortality (and increase in natality) seen in 1978-79 would correspond to the maternal cohorts born before 1957 (H1XH1). Mortality reverts from a fall to a rise during the 1980s (mostly H1), as the birth cohorts enter the H2 era in 1957 (H2XH1). After 1989-90 until 1996-98, the H3 circulation is highest, and mothers would have, on the average, been born between 1959-73, i.e. during the H2-H3 eras. The youngest (more H3) the cohorts, the highest the decline in mortality (H3XH3). After 1996-98, H1 and H3 viruses co-circulated (Finkelman *et al*., 2007), and the birth-cohorts also entered a period of co-circulation of H1 and H3 subtypes (after 1975), which makes the interpretation of trends more difficult if not impossible.

4. Discussion and Conclusions

It is proposed in this paper that early-life effects of influenza infection result, at the population level, in an acquired immune differentiation of successive birth-cohorts, both by adaptive epigenetic transformations capable of fitting fetal development to his/her new environmental condition (maternal infection and immune response), and by elimination of those genotypes unable to adapt. (For gene-environmental interactions, see Levins & Lewontin (1996) and Schmalhaussen (1949)). Due to the recycling of the influenza A antigens over time, both the rate of fetal survival to maternal infection and the "original antigenic sin" of the survivors would emerge, at the population level, as varying birth-cohort patterns of vulnerability to subsequent influenza re-infections and immune-inflammatory responses favoured by those selected phenotypes.

Of course, reality is probably much more complex than discussed here. Important antigenic differences may exist within each influenza subtype. In 1947, for example, there was no cross-protection to the 1947 H1N1 virus by vaccines containing the 1943 H1N1 strain (Kilbourne, 2006). So, current classifications of influenza viruses are possibly insufficient. We do not know as much about other types of human influenza viruses (B, C). Swine and equine influenza viruses have also infected humans, not to mention other viruses. But the evidence of cohort effects in secular trends of all-causes mortality unveiled by periods of circulation of specific influenza A subtypes is very impressive. As it is the correlation between periods of H1 and H2 circulation with increases in (CHD) mortality among cohorts born supposedly in years of H3 circulation.

In bygone times, transient patterns of population vulnerability known to be associated with epidemic occurrences were called 'epidemic constitutions'. The idea of 'epidemic constitutions' can be traced back to Sydenham and Boyle in the 17th century and even to Hippocrates (Creighton, 1891, p400).

The atmosphere was supposed to contain its postulated 'exciting' cause (Davey-Smith, 2002).

During the sequence of Cholera epidemics that hit the U.K. between 1831-32 to 1866, Sutherland (1850) contrarily to John Snow, was convinced that contaminated water had only a localizing role regarding the epidemic cases, but that it was not the epidemic primary cause (Davey-Smith, 2002; Snow, 2002). Along with many others, Sutherland believed that a different cause was necessary to explain the 'epidemic constitution'. A mechanism as simple as the one proposed here, based on just two elements — influenza priming and recycling of influenza subtypes — may be the explanation to those perceived 'epidemic constitutions', or in a more contemporary language, to the evolving population pattern of immune-inflammatory phenotypes (Finch & Crimmins, 2004) that, over time, recycle the causes of disease and death. Great influenza pandemics coincided with the emergence of cholera outbreaks in the U.K. and U.S. in 1830-33 (Langford, 2002). A quite serious influenza outbreak was also recorded in the U.K. in 1947-48, preceding the cholera epidemic described by Sutherland in that same year (Langford, 2002). And the same coincidence of influenza and cholera outbreaks is being reported now (Papua New Guinea, 2009).

Science always mistrusted and downgraded contingent events. But according to Gould (1996), the contingency's domain needs to be recognized in its true dimension: one as broad and important as anything deducible from natural law. "Contingent events, though unpredictable at the onset of a sequence, are as explainable as any other phenomena after they occur. The explanations as contingent rather than law-based do require knowledge of the particular historical sequence that generated the result, for such resolutions must be in the narrative rather than deductive model" (p36). That is the approach used in this study which might be called 'paleo-epidemiology'. It proved itself very fruitful, and it may advance our knowledge of many epidemiological problems that remain insufficiently explained until now.

For example, based on the rules displayed in Table 1 and on the assumption that upon influenza re-infections mortality would increase among cohorts primed by influenza A viruses of different subtypes and decrease among those primed by an equal subtype, the distribution of deaths across neighbour birth cohorts in years of well characterized influenza epidemics may give clues as to the recycling of influenza viruses in the past. This approach could, for example, clarify the differences in the epidemiology of CHD between the U.S. and the U.K. The data presented suggests that cohorts that in the U.S. were primed by H3 viruses (e.g. from 1890 to 1900) may have been primed mainly by H2 strains in the U.K. That would explain why the 1957-58 H2 epidemic was not as significant in the U.K. as it was in the U.S. H3 viruses may have circulated sooner in the U.K. (which would explain the comparatively higher U.K. mortality during the H1 epidemics of

1937, 1940 and 1951) and again just before 1900 and possibly after 1910, as described earlier, the cohorts more affected by the epidemics occurring during the H2 era. Differences in periods of circulation of the H2 and H3 subtypes in the U.S. and the U.K. during the end of the 19th century and the beginning of the 20th century would be expected, according to the hypothesis advanced here, to have cascading effects not only on differences in mortality, but also on differences in natality. They could, for example, explain part of the huge difference in reductions of live births in the U.K. compared to the U.S. in 1918-19, nowadays mostly attributed to effects of the war. And, as a consequence, they could be responsible for the huge difference in the numbers of life births 25-30 years later, a difference that significantly contributed to the disproportional aging of the U.K. compared to the U.S. population.

The implications of this hypothesis are manifold. The hypothesis may contribute to our understanding of the interplay between genes and environment in the constitution of the phenotypes, one of the main challenges of human geneticists interested in longevity, disease susceptibility, and behavior (Lewontin, 2006). But it goes beyond that. Human beings and other organisms adjust to their environments as populations (Gould, 1995; Dunn, 1960). According to Dunn,

> "The essential factor in biological adjustment is the differential representation of a variety of genotypes in successive generations. The action of natural selections and other evolutionary forces is inferred from observed changes in the frequencies of different genotypes."

But

> "What is inherited is a genetic constitution capable of responding, during its course of development, to the environment. The fate is not fixed in the fertilized egg, but gradually works itself out during development, depending on the latitude of response permitted by the inherited constitution and the environment." (Dunn, 1960, p787).

Thus, this hypothesis may also help us to understand how phenotypes produced and selected upon challenges contextual to one generation would affect the representation of available genotypes in the next one.

As demonstrated in the case of CHD trends, this study's few assumptions may be applied to analyze secular trends of other conditions, like pneumonias, tuberculosis, obesity and AIDS. For example, a consistent inverse relationship exists between trends of CHD, and pneumonia and influenza mortality (Figure 1). Every time that death from CHD increases, death from pneumonia and influenza decrease, and vice-versa. While CHD mortality is proposed to be triggered by H1 and H2 infections among H3 primed birth cohorts, rates of pneumonia deaths seem to increase during years of H3 epidemics, affecting preferentially non-H3 primed birth-cohorts (Azambuja,

2009a). Different combinations of priming and circulating viruses might be found to be associated with secular trends of other diseases.

While, at a first glance, this hypothesis could suggest biologic reductionism to those making efforts to advance our knowledge of social determinants of diseases causation, it can be seen as its opposite. Contrarily to the degenerative hypothesis that values averages and disregards variations as accidental realizations of an idealized type (Azambuja & Levins, 2007), this hypothesis relies on individuals' heterogeneity. Individuals submitted to the same environmental exposure are not expected to have the same risk of becoming sick because they acquired different vulnerabilities to it. And the emergence of the disease requires an interaction between vulnerability and a trigger capable of unveiling it. The hypothesis stresses aspects related with the temporal dimension of the diseases' occurrence, but it contributes to the incorporation of a concept of acquired vulnerability into causal modelling across other dimensions too (social, spatial, etc.).

Also, at a first glance, this hypothesis may be seen as introducing difficulties to the forecasting of trends. But this is not the case. The method employed here was eminently descriptive, because in this phase, that was the right approach to the problem. But, the combination of theory and observation results in a set of simple rules that may easily be used to predict future trends. Let us consider natality, for example. The rule is that disagreement between the influenza subtypes involved in maternal priming and maternal reinfection would increase fetal losses and decrease the number of live births. Considering an intergenerational interval of 25-30 years, if the new H1N1 subtype becomes dominant, we might expect increasing rates of natality during the next few years, considering that the mothers were mostly primed by H1 strains circulating in the 1980s. A transition would be expected in 5-10 years (assuming the persistence of H1N1 viruses) as the mothers' birth-cohorts enter the 1990s (see Table 2). The set of rules proposed here may be incorporated into mathematic models that may be adjusted using past occurrences. Those models could then be used to predict possible scenarios in the future upon alternative patterns of influenza circulation. The problem is that there are many gaps in our knowledge of the recycling of influenza viruses. This is why it would be necessary to take time to explore the mortality data with a paleoepidemiologic approach. But the stratification of periods and birth-cohorts in two or three blocks before their incorporation into models aimed at the prediction of longevity would benefit from knowledge of the influence of past influenza occurrences and dependence, by birth-cohort strata, on future patterns of influenza exposure.

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