Conections between causes of diseases:
Influenza and Sutherland's
"epidemiology of constitutions"

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This meeting

◆ Keeps with the UK tradition of joining demography, epidemiology, public health and medicine to reason about causality

◆ May recover the important debate among contagionists and noncontagionists about causes of diseases occurrences

◆ Sutherland, the Edinburgh Physician, and its quest for an epidemiology of constitutions

◆ Early 20th Century reports of birth-cohort effects in mortality and longevity

◆ the 2009 A/H1N1 Pandemic

This presentation is about what we see... and not see...

And about the powerful mental/cultural constraints that channel our view, called paradigms.

"*Once we recognize that the 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,
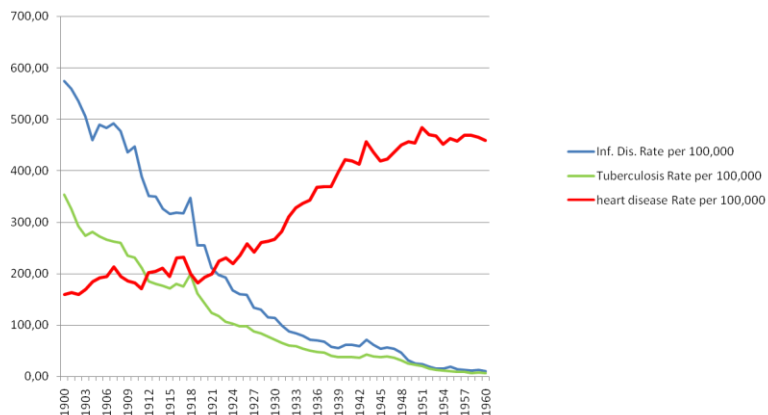apud Krieger, 2001:668.

Please, listen to this presentation as once instructed by Bacon (1597),

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

apud, Miettinen, 2001:592.

1960 - Rise in CHD mortality

Secular trends in selected causes of death.
Massachussetts, 1900-1960.

Legend:
- Inf. Dis. Rate per 100,000
- Tuberculosis Rate per 100,000
- heart disease Rate per 100,000

The beginning

An observer in 1960

- Post-war economic and technological development
  - urbanization
  - increase in access to goods
  - medical advances (antibiotics, vaccines, extension of medical care, decrease in infectious diseases and deaths)
  - automobiles, lack of exercise
  - high fat diets
  - stress
  - smoking

  FAVORING THE EMERGENCE OF
  CHRONIC DEGENERATIVE DISEASES

An observer after the 1970s

FIGURE 1. Age-adjusted death rates* for total cardiovascular disease, diseases of the heart, coronary heart disease, and stroke,† by year — United States, 1900–1996
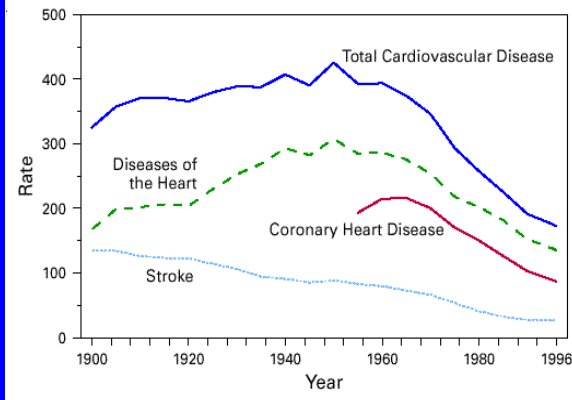
Rise and Fall?

EPIDEMIC !

MMWR, 1999

CHD EPIDEMIC

IF

- EPIDEMICS = temporal variations in occurrences

- OCCURRENCES = number of cases / population "at risk

- POPULATION **at risk** = % of **vulnerables** to exposure

- CASES = % population **exposed** X % population **vulnerables**

THEN

Look for a cause to a temporal variation in the population vulnerability to die from CHD !

Ecologic criteria of causality

Some occurrence
- limited in time...
- huge...
- happening, at least in part, before the beginning of the CHD epidemic
- global

Under the DEGENERATIVE paradigm?

- genetics? No, short period of time...

- negative selection of WW I and II survivors? not huge enough...

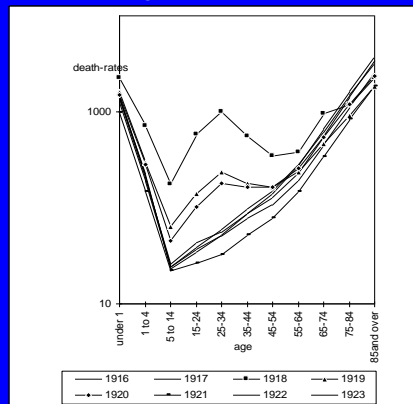- smoking - contributory?...

- ?????

1918-19 INFLUENZA

Annual mortality (/100,000) from Influenza and Pneumonia in the Registration States. US, 1900-1940.
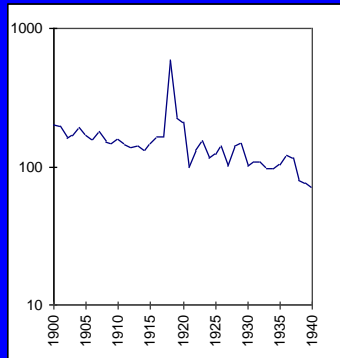
Source: Gover M, USPHS. Pub Health Rep 1943; 58:1033-1061.
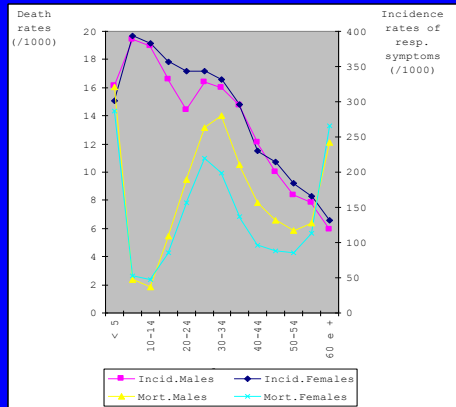
1918-19 INFLUENZA

Death-rates (/100,000) from Pneumonia and Influenza by age. US Death Registration States, 1916-1923.

Source: Linder FE, Grover RD. Vital statistics rates in the United States - 1900-1940. National Office of Vital Statistics. US Public Health Service.US Government Printing Office, Washington, 1947.

1918-19 INFLUENZA

Morbidity and mortality due to Influenza and Pneumonia by age and sex. US, 1918-19.

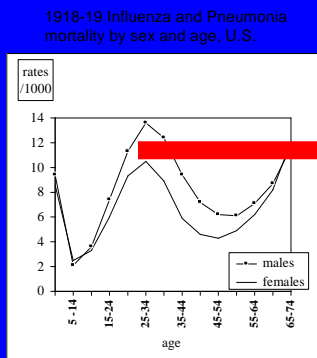Sources: Mortality: Crosby AW. America's forgotten pandemic: the influenza of 1918.New York, NY:Cambridge University Press; 1989.
Morbidity:Britten RH. The incidence of Epidemic Influenza, 1918-19. Pub Health Rep 1932; 47:303-39.
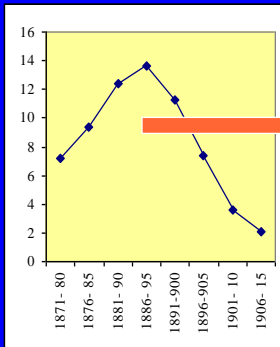
"Reasoning"

If a CHD "iniciation" was associated with the age-distribution of the 1918-19 influenza pandemic...

... Then, CHD mortality must have varied along the correspondent birth cohorts
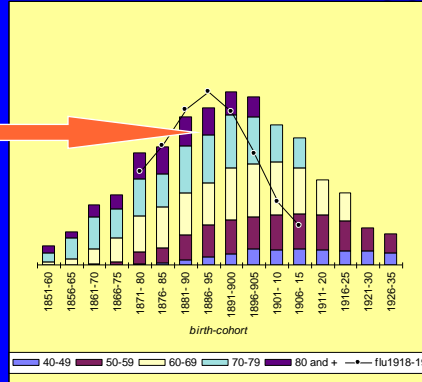
Result : the Rise in CHD mortality

Birth-cohort distribution of **FLU mortality**. Men, US, **1918-19**


whites
males and
born around 1900

Birth-cohort distribution of **CHD deaths**, Men, US, **1920-85** **(stand. to the 1940 pop)**
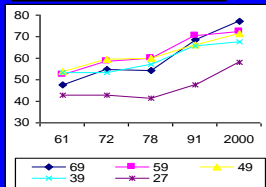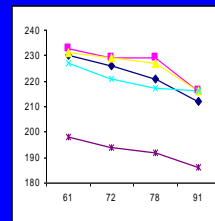

whites
males and
born around 1900

Aterogenesis: more then one mechanism
CHD : **more than one disease**
CHD TREND: combination sub-population of cases

FIGURE 1. Age-adjusted death rates* for total cardiovascular disease, diseases of the heart, coronary heart disease, and stroke,† by year — United States, 1900–1996

High Cholesterol

Low HDL
High Triglycerides

Inflammation

"Degeneration"
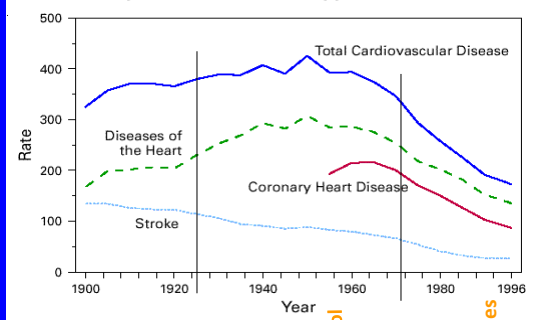
Inflammation

Average level of serum cholesterol by age. USA, 1960-62 à 88-94.

Prevalence of overweight by age. USA, 1960-62 to 2000. NHS, NHANES

CHD 1960 and 2000

Same or *different* nosologic entities ?

1960

- high mortality rates
- high lethality
- 2/3 of deaths, sudden
- large vessels disease
- hypercholesterolemia
- "degeneration"

2000

- 60% decline in mortality rates
- lower letality
- decrease in sudden deaths
- small vessels disease
- insulin resistance phenotype
- inflamation

Summary

- **The term CHD encompasses more then one disease.**

- **CHD mortality trends represents a varying combination of types of CHD over time.**

- **The impressive decline in CHD mortality since the late 1960s was consistent with the observed decline in the average serum cholesterol level of the US population.**

- **As CHD mortality falls, a new atherogenic phenotype (related with insulin resistance) becomes more prevalent.**

Summary

- Changes in population average serum cholesterol levels has been unsatisfactorily explained by changes in EXPOSURE to high-fat diets.

- Mimicry between the viral HA and the apoB LDL or the LDL receptor (suggested to exist in some strains) might provide the link to increased cholesterol levels

- Cross-reactive auto-immune responses to influenza re- infections might explain both, the 1918 H1 Pandemic lethality and the high rates of CHD deaths seen in cohorts born around 1890 and supposedly primed by H3 viruses

Summary

- The 1918 Influenza Pandemic had the width, precedence and demographic characteristics to be proposed as associated with the CHD epidemic. Its impact was greater in whites, men and cohort born around the year 1890 – the same groups with higher CHD death-rates from 1920-85.

Summary

- **Cross-reactive auto-immune responses to re-infections might explain the historical registries of high rates of CHD deaths seen in members of those "initiated" birth-cohorts (born around 1890) during Influenza Epidemics**

New developments

- ◆ The fall in CHD deaths
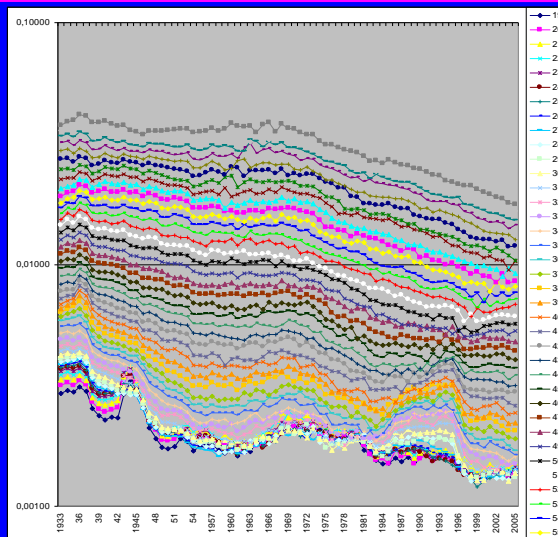- ◆ a bigger role for influenza?

Co-evolution of CV and Respiratory Diseases mortality, and its relation with Influenza.
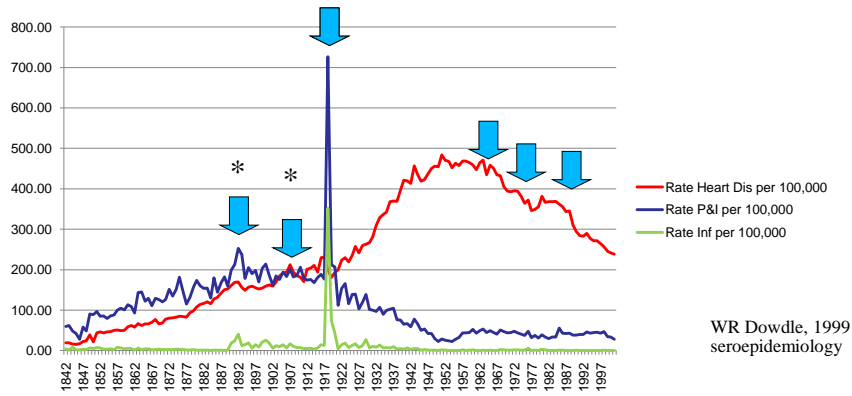
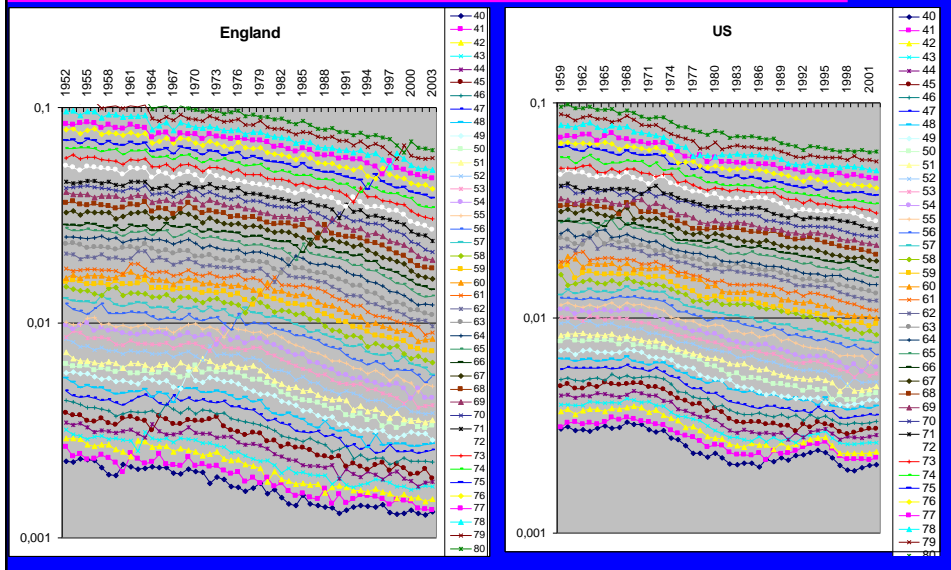Massachussetts, Estados Unidos, 1842 a 1999.
Fonte: Massachusetts Department of Public Health, Registry of Vital Records and Statistics, April 26, 2004
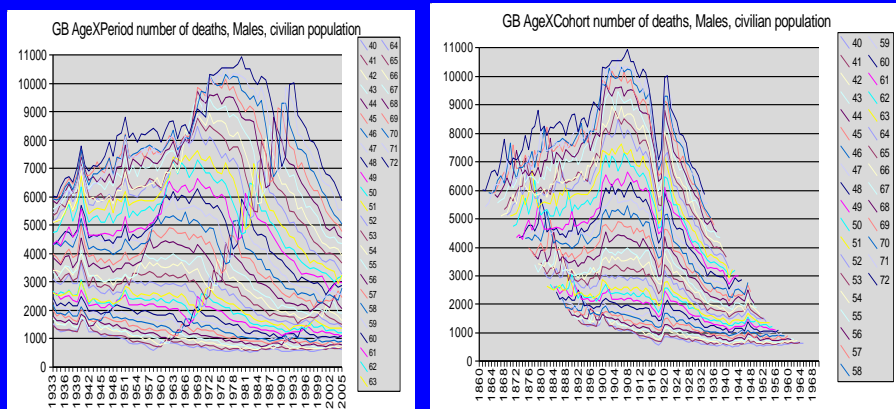
US yearly annual mortality, by age

Source: HMD

Yearly mortality rates.

England

US

United Kingdon - yearly number of deaths 1933-2005

GB AgeXPeriod number of deaths, Males, civilian population

GB AgeXCohort number of deaths, Males, civilian population
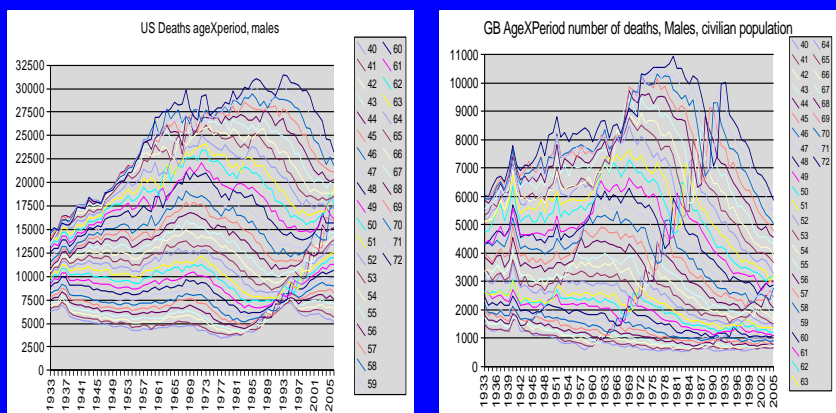
Source: Human mortality database

What is best to observe mortality trends: rates or number of deaths?
(Bruce Cairns (2004) – demographic selection – mixtures of sub-populations

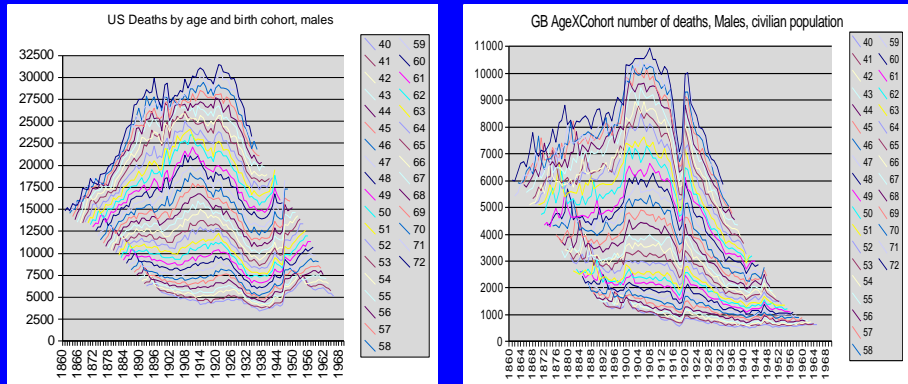US yearly number of deaths, 1933 - 2005
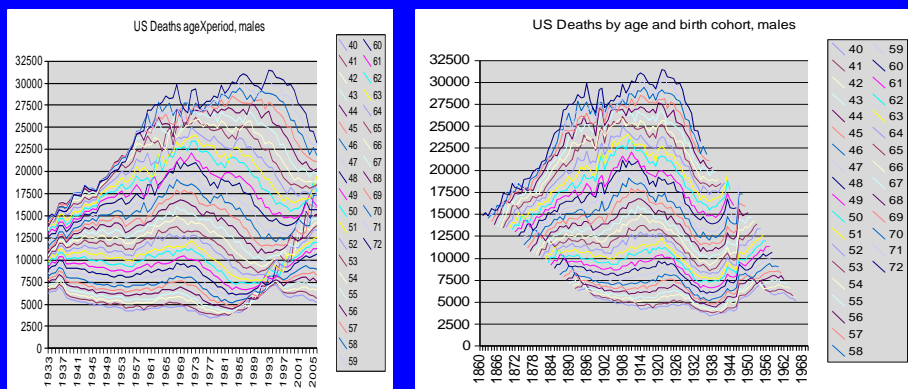
US Deaths ageXperiod, males

US Deaths by age and birth cohort, males

Source: HMD

US and UK number of deaths 1933-2005

US Deaths ageXperiod, males

GB AgeXPeriod number of deaths, Males, civilian population

Source: HMD

US and UK number of deaths 1933-2005

US Deaths by age and birth cohort, males

GB AgeXCohort number of deaths, Males, civilian population

Source: HMD

Secular trends in number of births and in infant mortality ratios, Massachussetts, 1885-2000
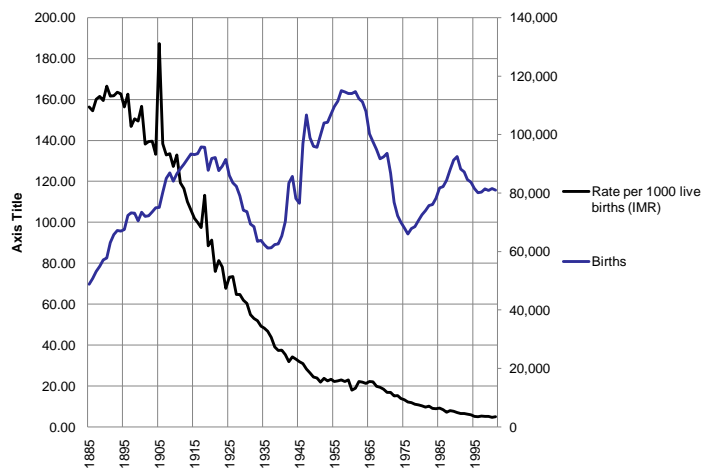
Legend:
- Rate per 1000 live births (IMR)
- Births

Massachussetts, Estados Unidos, 1842 a 1999.
Fonte: Massachusetts Department of Public Health, Registry of Vital Records and Statistics, April 26, 2004
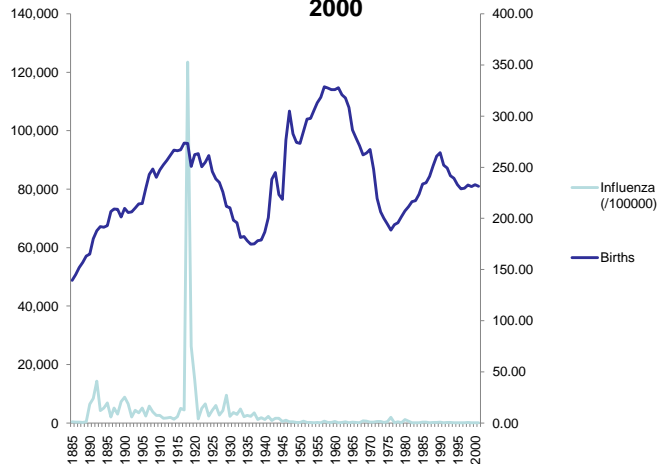
Seculat trends in number of births and in in influenza death-rates, Massachussetts, 1885-2000

Massachussetts, Estados Unidos, 1842 a 1999.
Fonte: Massachusetts Department of Public Health, Registry of Vital Records and Statistics, April 26, 2004

Developmental origins of disease – Lawlor

Developmental modification - (Schmalhausen, Levins & Levontin)

- if it falls outside of the norm of reaction: eliminated by the genes

- Absence of modification/adaptation in face of a new environmental challenge (new virus): eliminated by the environment (virus)

- Positive selection: viable modification (within the space of the norm of reaction) more adapted to the environment (circulating viruses) survive and reproduce (and transmits its genes)

- When a new challenge occurs – new strain – the surviving adapted/modified organism (and its progeny) may have a smaller genetic space available to adapt or not... Less adaptation, more deaths (pre or post-natal (inadequate immune response to a different strain?)

Influenza may have a role in the modification of inheritance

Conclusions

◆ The whole population may be a better place to identify significant changes in influenza viruses than laboratories.

◆ Changes show theselves, both as determinantes of epidemics (period effect) and of birth-cohort priming (birth-cohort effect). Population outcomes (increase or decrease in number of deaths by all and specific causes) result from interactions between aquired vulnerabilities (cohort) and environmental triggering (period effects)

Epidemiology of the Constitutions

◆ Sutherland was right
◆ Exposure to an infectious agent is not enough to explain epidemics, or even individual cases.
◆ It is the invisible "population constitution" that determines the size and distribution of the effect of each specific environmental challenge
◆ Influenza may have an important role on its relatively frequent modifications

Conclusions

This is not to say that other determinants of vulnerability are not important. They are, but influenza may be the main determinant of the

secular trends
in THE POPULATION
built vulnerability

to diseases and deaths occurrences

Paradigm shift

2009 A/H1N1 Influenza

- This will be a good moment to test some possibilities.
- Wouls H2 and H3 cohorts born after 1957 until 1976, and intermingled with H1 (and B?) cohorts after that, increase their CVD outcomes during the next years, in case of persistence of the new virus?
- Would H1 Cohorts (born before 1957) have gains in longevity?
- Would natality increase?