Determinants of Influenza Mortality Trends in U.S. 1960-2010

Enrique Acosta¹, Matthew S. Miller², Stacey A. Hallman³, Robert Bourbeau¹, D. Ann Herring⁴, David J.D. Earn⁵, Joaquin Madrenas⁶ and Alain Gagnon¹

¹Département de Démographie, Université de Montréal, ²Department of Biochemistry, McMaster University, Hamilton ³Department of Sociology, Western University, London, ⁴Department of Anthropology, McMaster University, Hamilton, ⁵Department of Mathematics and Statistics, McMaster University, Hamilton, ⁶Department of Microbiology and Immunology, McGill University

Extended Abstract

Introduction

The 2009 flu pandemic outbreak showed that influenza remains a significant health threat, well into the 21st century. About a century before, the Spanish Flu (1918-1920), also known as the “mother of all pandemics” (Taubenberger and Morens 2006), caused more deaths than the First World War and killed more people in 20 weeks than AIDS did in 20 years.

Influenza mortality has declined considerably, although not consistently, during the last half century for most age groups (figure 1) in United States. However, the causes responsible for these variations are still not clear and vary widely depending on the theoretical framework employed.

The Omran’s epidemiological transition theory has put forward a framework to interpret and accounts for the replacement of infectious diseases by chronic diseases due to expanded public health and sanitation. In this framework, mortality declines from infectious diseases are mainly driven by period factors in the short term, such as environmental changes, medical innovations and public policies. In contrast, chronic and degenerative disease mortality changes are mainly driven by long term cohort factors resulting from both the cumulative risks and cumulative advantages over the life-course (Omran 1971; Olshansky and Ault 1986).

Alternatively, the technophysio evolution theory proposes that not only are chronic and degenerative diseases highly affected by cohort factors but so too are infectious diseases. This theory proposes that as new cohorts are born, their physiological capital increases due to cumulative cycle of improving nutritional
and sanitary environments in early life and intergenerational epigenetic transmission of physiological enhancement by the mother (Floud et al. 2011).

In addition, the antigenic imprinting theory proposes that influenza mortality variations are in part explained by the interaction between previous exposures to specific influenza subtypes during early life—that would have primed the immunological system- and the specific virus subtype encountered later in life (Gagnon et al. 2013). This interaction could either decrease or increase mortality risks, depending on the degree of compatibility or incompatibility between the virus subtypes. Given that most individuals in a yearly cohort are exposed to the same virus subtype during the first years of life, there would be specific yearly cohort effects stemming from antigenic drifts and shifts. This differential priming of cohorts within a population could be seen as a population-level signature of antigenic imprinting (Ma, Dushoff, and Earn 2011). Strong evidence of antigenic imprinting has been observed in studies of the age structure of mortality during influenza pandemics (Oeppen and Wilson 2006; Gagnon et al. 2013; Hallman and Gagnon 2014; Gagnon et al. 2015).

Two important questions arise from the mechanisms discussed above: First, what is the role of each of these mechanisms in the influenza mortality variation during the last decades? Second, is the reduction of mortality from influenza in the last decades a cohort or a period phenomenon? This study aims to address these questions and to test hypotheses about the role of period and cohort effects in recent influenza mortality trends in the light of the discussed theoretical perspectives.

**Data and Methods**

Counts of age-specific monthly mortality by cause and sex in the U.S. between January 1959 and December 2010 were taken from the National Center for Health Statistics (2015). The annual age-specific population at risk was obtained from the Human Mortality Database (2015) and the monthly age-specific population at risk was estimated through interpolation, accounting for differences in monthly durations.

Estimation of influenza mortality is challenging since deaths caused directly or indirectly by influenza exposure are not always registered under the specific category of influenza. Pneumonia, and complications of the circulatory and respiratory systems, can be triggered by influenza infection yet influenza may not be recorded as the underlying cause.

A method widely used to estimate influenza mortality is Serfling regression. We use a variation called the Serfling negative binomial cyclical regression model, which allows for the calculation of influenza mortality taking into account seasonal and secular mortality trends (Thompson et al. 2009). The basic formulation is:

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\log(\text{deaths}_{a,s,t}) = \sum_{i=0}^{5} \beta_i t_i + \beta_6 \sin\left(\frac{2\pi t}{12}\right) + \beta_7 \cos\left(\frac{2\pi t}{12}\right) + \log(\text{exposure}_{a,s,t}),
\]

where \(a\) is age (0, 1, 2, ..., 100), \(s\) is sex, \(t\) is the epidemic period (from the 1959-1960 to the 2009-2010 seasons), \(\text{deaths}_{a,s,t}\) are death counts and \(\text{exposure}_{a,s,t}\) is the population at risk. The Serfling negative binomial model includes three principal components: \(\sum_{i=0}^{5} \beta_i t_i\) controls for secular trends in mortality, while \((\beta_6 \sin\left(\frac{2\pi t}{12}\right) + \beta_7 \cos\left(\frac{2\pi t}{12}\right))\) captures for influenza seasonality and \(\log(\text{exposure}_{a,s,t})\) tracks changes in age-structure over time.

In order to identify independent age, period and cohort effects within the secular trend of influenza mortality, we used the Intrinsic Estimator (IE) method. This method was developed by Yang et al. (2004),
with the purpose of getting around the well-known identification problem caused by the perfect collinearity within a model containing fully dependent variables, as the case of age, period and cohort ($\text{cohort} = \text{period} - \text{age}$). Given the model limitations related to the amount of coefficients to estimate, we aggregated mortality data into 5 year groups for age, periods, and cohorts.

The IE method is used to identify independent effects of secular trends in the wider scale, such as when analysing the mechanisms of the technophysio evolution theory. However, analyses of antigenic imprinting mechanisms need a finer resolution of single year cohorts because influenza virus subtypes vary from one epidemic year to the next one. For example, in the case of the aggregated 5-year scale, the 1965-1969 cohorts would be treated as homogeneous group when in reality the 1965-1967 cohorts would have been primed by AH2N2 subtype and 1968-1969 cohorts by the AH3N2 subtype.

Therefore, with the purpose of improving resolution and identifying variations caused by the antigenic imprinting mechanism, we constructed a lexis surface at the single year level. This visual tool allows us to identify potential age, period, and cohort effects with the naked eye. An innovative aspect of this approach is the analysis of excess mortality caused by influenza at the single-year resolution that can simultaneously account for age, period, and cohort effects. Further analysis using p-spline smoothing models on influenza mortality are in progress to complement these analyses.

**Preliminary findings**

Age, period, cohort analyses made for pneumonia and influenza mortality (figure 2) show a strong predominance of cohort effects over period effects in the long term influenza mortality trend.

![Figure 2. Intrinsic Estimates of period and cohort effects of pneumonia and influenza mortality](image-url)

With regard to single-year cohort effects, we expected significant cohort effects for the pandemic cohorts of 1890, 1918, 1957, and 1968. However, preliminary results show cohort effects only for the 1932 and 1946 cohorts (figure 3). Important drifts of AH1N1 virus during these epidemical seasons could have either primed or caused insults to those cohorts, leaving long term consequences face to subsequent influenza epidemics exposure. Other cohort effects shown in figure 3 seem to be the result of the misreporting of age at the time of death, representing heaping related not with age but with rounded years of birth (for example, 1890, 1900, and 1910).
Discussion and conclusion

The preliminary findings reported here potentially have important implications. On the one hand, they suggest that the mechanisms proposed by the epidemiological transition, technophysio evolution and antigenic imprinting theories are not necessarily mutually exclusive as engines of mortality variations. They seem to even act simultaneously, triggering different mortality changes at distinct levels or scales. On a wider scale, influenza mortality decline is driven by medical and public policies improvements during specific periods by increasing health capital over succeeding cohorts. On a finer scale, the characteristic irregularity of influenza mortality decline is mainly caused by the interaction between the signature of antigenic imprinting of the population and the specific virus subtype circulating during each period. In other words, mortality variations caused by antigenic imprinting could represent small variations inside a longer term mortality trend.

On the other hand the finding of cohort predominance in long term influenza mortality variations is contrary to the common contemporary assumption of the dominance of period over cohort effects in terms of the factors influencing the reductions in infectious disease mortality. This is consistent with the technophysio evolution theory as they reflect the increasing improvement of physiological capital for successive cohorts. These findings suggest that cohort effects could be driving changes in mortality from infectious diseases such as influenza, as well as mortality caused by chronic and degenerative diseases. This dominance of cohort effects would be the logical result of the virtuous cycle of continuing improvements of nutritional and sanitary environments during early life, decreasing infectious diseases in childhood that leads to improved nutrient absorption, increased physical robustness, better cognitive development, educational attainment and economic performance as well as to the intergenerational transmission of physiological improvements (Floud et al. 2011; Robert W. Fogel 2003; R. W. Fogel and Costa 1997).

These results highlight the importance of early life conditions not only for reduction of chronic and degenerative mortality, but also for enhance survival face to infectious diseases. However further analyses with infectious diseases other than influenza are necessary in order to be able to generalize these findings.
References


