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Influenza-Associated Excess Mortality in South Korea

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Abstract

Introduction—It is important to determine the health impact of influenza in order to calibrate public health measures. The objective of this study was to estimate excess mortality associated with influenza in Korea in 2003–2013.

Methods—The authors constructed multiple linear regression models in 2014 with weekly mortality rates stratified by age, region, and cause of death against weekly surveillance data on influenza virus collected in 2003–2013. Excess mortality rates were estimated using the difference between predicted mortality rates from the fitted model versus predicted mortality rates with the influenza covariate for each strain set to 0.

Results—During the study period, influenza was associated with an average of 2,900 excess deaths per year. The impact of influenza on mortality was significantly higher in older people; the overall all-cause excess annual mortality rate per 100,000 people was 5.97 (95% CI=4.89, 7.19), whereas it was 46.98 (95% CI=36.40, 55.82) for adults aged ≥65 years. It also greatly varied from year to year, ranging from 2.04 in 2009–2010 to 18.76 in 2011–2012.

Conclusions—The impact of influenza on mortality in Korea is substantial, particularly among the elderly and the rural population. More-comprehensive studies may be needed to estimate the full impact of influenza.

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Introduction

Influenza virus poses a significant public health threat, infecting about 5%–10% of adults and 20%–30% of children worldwide every year.¹ Although most infections are associated with mild and self-limiting disease, a small fraction of infections lead to severe disease or even fatality. Individuals with underdeveloped or compromised immune systems or pre-existing chronic conditions are at an increased risk of developing serious or life-threatening complications following an influenza virus infection. It is estimated that influenza causes between 0.25 and 0.5 million deaths around the world each year,² as well as a far greater number of hospitalizations and ambulatory consultations.^{3–5}

One commonly used measure of the burden of influenza is the mortality impact, which can be measured either directly using the number of deaths with laboratory confirmation of influenza virus infection, or indirectly using statistical models.^{6–12} The direct approach tends to underestimate the total impact of influenza on mortality because it neglects deaths caused by influenza but not diagnosed or laboratory confirmed,^{13,14} as well as deaths from exacerbation of pre-existing chronic diseases triggered by influenza virus infection and therefore not coded as having been caused by “influenza.”¹⁵ Statistical models can provide more complete assessment of the impact of influenza on mortality by estimating the number of deaths that would have occurred if influenza had not circulated, accounting for seasonality and other relevant factors.^{11,13,14,16–21} This measurement of influenza mortality burden from these statistical models is generally referred to as the “excess mortality” estimate.

Using statistical models, various studies from different countries have reported varying all-age excess mortality rate attributable to influenza typically in the range of 8–26 all-cause deaths per 100,000 people per year.^{6–11,13,14,16,18–25} However, there are relatively few published estimates of excess mortality in Asian countries, and no study has yet quantified the excess mortality impact of influenza in South Korea (hereafter Korea). The objectives of this study were to estimate influenza-associated excess mortality in Korea, from 2003 through 2013, and to examine patterns in excess mortality by age, influenza type/subtype, and geographic area.

Methods

Data Sources and Measures

The authors obtained individual mortality data from 2003 through 2013 compiled by the Korea Statistics Micro-Data Service System.²⁶ The data set contained detailed demographic, geographic, and socioeconomic characteristics for each included case. Causes of death were coded based on the ICD-10. A marked increase in mortality during influenza seasons, particularly among people aged >65 years with comorbidities, has been documented consistently in numerous studies.^{16,17,27–29} In order to account for other deaths that may have been precipitated by influenza but coded in the vital statistics as resulting from other causes than influenza, the following seven major underlying causes of death found to be strongly related to influenza from previous studies^{16,17} were selected to estimate impact of influenza on mortality rates: respiratory diseases (J00–J99), cardiovascular diseases (I00–

I99), malignant neoplasms (C00–C97), diabetes mellitus (E10–E14), kidney diseases (N00–N07, N17–N19, N25–N27), chronic liver diseases (K70, K73–K74), and degenerative disease of nervous system (G30–32). This study used deaths caused by land transport accidents (V01–89) as a control outcome in the model. All other underlying causes except for the seven major causes of death were combined and categorized into the group, “other causes.” Any death that took place outside Korea (i.e., deaths of Korean citizens that occurred elsewhere) was excluded from analysis.

Age- and province-specific mid-year population estimates for 2003–2013 were collected from the Statistics Korea²⁶ database to permit estimation of mortality rates and excess deaths rates per 100,000 people per year. A smoothing cubic spline interpolation method was applied to the annual population between 2002 and 2014 with a knot at each data point (t_i , for $i=1, \dots, 13$) to obtain daily population estimates in 2003–2013, which later were averaged to weekly population sizes by age group and province.

Weekly virologic surveillance data were extracted from weekly and annual reports published by the Korea Influenza Surveillance Scheme.³⁰ This web-based network comprises 862 clinics and hospitals reporting the proportion of patients who visited with influenza-like illness (ILI) symptoms—defined as having an acute fever of $\geq 38^\circ\text{C}$ and cough or sore throat—on daily or weekly basis, and 93 laboratories participating in the Korea Influenza and Respiratory Viruses Surveillance System, which reports weekly detection rates for each type and subtype of influenza virus and other respiratory viruses.³⁰ Weekly ILI consultation rates were publicly accessible on the Infectious Disease Web Statistics System website managed by the Korea Centers for Disease Control and Prevention.³¹ As previously proposed and applied in other studies,^{16,17} a weekly indicator of the incidence rate of influenza virus infections by type/subtype was derived by multiplying the proportion of ILI patients who visited participating sentinel clinics by the proportion of respiratory specimens testing positive for each influenza type/subtypes in the week as:

$$Flu_i(t) = \%ILI(t) \cdot \%Positive_i(t)$$

Here, the authors refer to this composite variable $Flu_i(t)$ as the “proxy” for influenza activity for each strain i on week t .

Data on daily temperature and relative humidity in each province for the study period were collected from the archives of the Korea Meteorological Administration.³² Weekly average temperature and relative humidity were compiled to calculate absolute humidity,¹⁷ which has been found to be associated with influenza activity.^{33,34} Additional demographic, socioeconomic, and other information on each province were collected from Statistics Korea.²⁶

Statistical Analysis

A generalized additive model was used to estimate excess mortality rates based on the difference between predicted mortality rates from the fitted model versus predicted mortality rates with the influenza covariate for each strain set to 0.^{16,17} Weekly mortality rates $M(t)$

were stratified by age, administrative region, and cause of death, and were regressed against weekly influenza incidence proxies for each strain $Flu_i(t)$ as below:

$$M(t) \approx \sum_i \lambda_i \cdot (1 + A_1(t - t_0)) \cdot Flu_i(t) + \beta_{pH1} \cdot (P \cdot Flu_{pH1}(t)) + \beta_B \cdot (P \cdot Flu_B(t)) + \text{Baseline}(t)$$

A 1-week lag on all covariates was applied in the regression model to take into account an interval between the typical time of diagnosis or disease onset and the time of death ($t = t - 1$).

$$\text{Baseline}(t) = f(t, df) + f(H_t, df)$$

The incidence proxies for the various influenza types/subtypes on week t were scaled by multiplying each proxy by a factor of $(1 + A_1(t - t_0))$, based on the assumption that the overall influenza surveillance system was constantly improved (e.g., by restructuring the surveillance network) over the first few years from 2003 to 2008 when the government replaced all public clinics with private sentinel clinics for: (1) a better representation of the population with more-diverse patient groups; and (2) the better quality of surveillance data provided by private clinics in the previous years. Here, λ_i are the regression coefficients for the scaled influenza incidence proxies $(1 + A_1(t - t_0)) \times Flu_i(t)$, where t_0 refers to the week in which the major structural change to the influenza surveillance system was made ($t_0 = 279$). The incidence proxies for viruses circulating during the period of the A(H1N1) pandemic in 2009 were adjusted by another scaling factor denoted as P to account for artificially higher virus activities possibly resulting from an elevated level of public health alerts during the period from April 2009 to April 2010. P was set to 1 for $305 \leq t \leq 357$ and 0 prior to and after the period. Weekly absolute humidity was also included in the regression models as a covariate to examine its potential association with estimated influenza activity and mortality rates. Denoted as (t) and (H_t) , a cubic spline smoother was used in this non-parametric function to summarize the trend of the weekly death rates as a function of weekly calendar time and absolute humidity, respectively. Separate models were constructed for each time series of cause-specific deaths.

For ease of presentation, the authors defined each influenza season in Korea to include Week 26 to Week 25 of the subsequent year until 2007–2008, and from Week 35 to Week 34 of the subsequent year starting from the 2008–2009 influenza season, owing to recent changes in the timing of influenza virus epidemics. Excess mortality was then estimated for each influenza season. To assess and compare death rates in 16 administrative regions across the country, age-standardized excess mortality rates were calculated adjusting for difference in the age structure of the populations. Bootstrapped CIs were obtained for each estimate by fitting the residuals in the autoregressive moving average model. All statistical analyses were performed in 2014 using R, version 3.1.0.

Results

From 2003–2004 through 2012–2013 (10-year period), a total of 2,570,939 deaths were reported in Korea, with an average crude mortality rate of around 10 deaths per 100,000 people each week, and a slightly higher mortality rate during the winter (Appendix Figure 1). During this period, Korea experienced two influenza epidemics in most years, with the first peak in the early winter (December through January) followed by a smaller peak in the late spring (April through May). The pandemic influenza A(H1N1) virus emerged in 2009 (denoted “pH1N1”) has replaced the preceding seasonal influenza A(H1N1) subtype (denoted “sH1N1”) since 2009.

Based on the fitted regression model with $R^2 > 82\%$, influenza was associated with an excess of approximately 2,900 deaths on average each year in Korea, accounting for about 1.2% of all deaths in a given year. The average annual influenza-associated excess mortality rate was 5.97 per 100,000 people for all causes with annual estimates ranging from 2.04 in 2009–2010 to 18.76 in 2011–2012 (Table 1). The overall excess mortality was higher in years in which A(H3N2) was predominantly circulating. It was estimated that 3.84 all-cause deaths per 100,000 people were associated with infection of influenza A(H3N2); sH1N1 and influenza B caused an average of 0.76 and 1.45 excess deaths per 100,000 people each year, respectively. The estimate for pH1N1 was smaller and not statistically significant.

The estimated all-cause mortality rate associated with any influenza virus infection was highest in the elderly (aged ≥ 65 years) and middle-aged adults aged 45–64 years, with an average of 46.98 and 2.73 excess deaths per 100,000 people, respectively (Table 2). Influenza A(H3N2) accounted for most influenza-associated deaths in the elderly with an average of 31.94 excess deaths per 100,000 people. An impact of influenza B on all-cause excess mortality was more likely to be detected compared with other influenza types or subtypes in older children and young adults.

Annual estimates of cause-specific excess mortality are summarized in Table 3. Deaths caused by seven major causes, including respiratory, cardiovascular, cancer, diabetes mellitus, renal, chronic liver, and degenerative nervous system diseases, accounted for almost 70% (4.16/5.97) of the all-cause excess mortality attributable to influenza. Specifically, respiratory and cardiovascular diseases contributed about 46% (2.75/5.97) of all influenza-associated deaths each year, with an average of 1.34 and 1.41 excess deaths per 100,000 people, respectively.

This study examined excess deaths attributable to influenza in all 16 cities and provinces of Korea (Appendix Table 1, Appendix Figure 2). There was a significant difference in age-standardized all-cause excess mortality rates between and across different cities and provinces, ranging from a low about 2.17 for Daejeon to a high about 15.68 per 100,000 people for Jeonnam province. Overall, the mortality burden attributable to influenza appeared to be significantly higher in province-level administrations than in metropolitan cities, with an average of 8.09 and 4.10 deaths per 100,000 people, respectively. Similar patterns were observed in the influenza-attributable fractions of mortality in different study areas with less variability (Figure 1).

Discussion

This is the first study to report influenza-associated excess mortality in Korea, estimating that influenza was associated with around 2,900 deaths per year, and 1.2% of all deaths during 2003–2013. Mortality impact of influenza was particularly higher in individuals aged 65 years and older and years in which A(H3N2) was predominantly circulating, which is consistent with other studies.^{12,17,35,36} It may well explain an unusual, sharp peak in excess mortality from 2.94 in 2010–2011 to 18.76 in 2011–2012 in which there was a noticeable increase in the crude, all-cause mortality during the influenza season and A(H3N2) re-emerged as a predominant strain after two consecutive pH1N1 predominant years. The mismatch of the vaccine strain and the predominant circulating strain in 2007–2008 might be one of the factors contributing to the high excess mortality burden estimated in that season in which 95% of sH1N1, 98% of A(H3N2), and 92% of B strains that were isolated did not match the vaccine strain.³⁰

Compared with seasonal influenza viruses, pH1N1 was associated with low or modest excess mortality during 2009–2010 and 2010–2011. This study estimated that there were 572 all-cause deaths associated with pH1N1 in the first pandemic wave in 2009–2010, which compares to 270 laboratory-confirmed deaths.³⁷ This is consistent with the notion that indirect estimates of impact generally identify a higher burden than direct estimates based on laboratory-confirmed outcomes. The overall estimate of excess mortality for all ages was higher in the second wave in 2010–2011 than the first wave in 2009–2010 (Table 1), despite the prolonged duration of the first wave that lasted for 40 weeks in total (Appendix Figure 1). The low impact of pH1N1 was also reported in other studies,^{10,13,14,18,19} and could be attributed in part to wide-scale use of antivirals³⁸ and monovalent pH1N1 vaccines (14.3 million people or 84% of the vaccinated “priority groups”)³⁹ during the first wave, when it should be noted that deaths in young adults during the pandemic still represented a substantial impact even without the high number of excess deaths in the elderly seen in other years. For example, Viboud and colleagues⁴⁰ estimated the total years of life lost attributable to influenza during the 2009 pandemic in the U.S. to be comparable to that from the 1957 and 1968 pandemics, despite a relatively smaller number of excess deaths. Antiviral drugs were distributed for free among all high-risk individuals with ILI symptoms and later on to all individuals with acute febrile respiratory illness. This aggressive use of antivirals particularly during the initial wave may have substantially reduced morbidity and mortality attributable to pH1N1.

The contribution of influenza to several underlying causes of death (Table 3) is similar to that found in the U.S. study,¹⁶ with cardiovascular diseases carrying the greatest proportion of all influenza-associated deaths, followed by respiratory diseases and cancer. Only about 22% (1.34/5.97) of all influenza-associated deaths in Korea were due to respiratory causes including influenza and pneumonia, which is significantly lower compared with the U.S. (30%)¹⁶ and Hong Kong (53%).¹⁷ However, as documented in other studies,^{41,42} this could be potentially due to variation in coding practice across countries (e.g., respiratory diseases more or less likely to be coded as the underlying cause of death among patients with multiple chronic conditions) rather than a true difference in etiology of deaths or the consequences of influenza virus infections on mortality in different places.⁴³

The average annual mortality impact of influenza in Korea that this study estimated was slightly lower than estimated in some other countries, but still represents a substantial burden on all-cause mortality. Under an assumption that vaccine effectiveness is similar in Korea to elsewhere,⁴⁴ the lower overall estimate of impact might partly be explained by high influenza vaccination coverage across the country. For example, between 2011 and 2013, population coverage of influenza vaccination was 43% in Korea.²⁶ Among people aged 65 years and older, the coverage was around 79%, which well exceeds the average of Organisation for Economic Co-operation and Development countries (51%) and other countries such as Denmark (44%) and the U.S. (67%).⁴⁵

It may be worthwhile to note that Jeonnam province was found to have both the highest excess mortality and the highest age-standardized vaccination coverage. One of the possible reasons for such high mortality burden in Jeonnam could be the relatively high all-cause death rate as well as the high fraction of influenza-associated deaths from cancer and cardiovascular diseases found in some previous studies.^{16,17} In addition, national statistics showed that among all 16 administrations, Jeonnam has the highest overall mortality rate, highest proportion of elderly (more than 20% aged 65 years and older compared with the national average of 12%),²⁶ highest median age, but lowest median household income (Appendix Table 2), which might to some extent contribute to the relatively high influenza-associated mortality burden observed in this province in this study.

Limitations

The present study had a few limitations. The incidence proxy used to estimate influenza activity may not have accurately represented the true incidence for the following reasons. First, clinical and laboratory influenza surveillance data were only available at the aggregate level (i.e., no age-specific data), which may have introduced bias to the estimates. Second, ILI sentinel surveillance has been improving over the study period whereas the ILI reporting rates among sentinel clinics was low and inconsistent with a high “zero-reporting” rate during the first few years of the study period.³⁰ Use of surveillance data for influenza activity in the model might have caused underestimation or overestimation of the mortality burden, although the authors accounted for this in the regression model with scaling factors. Third, some residual effect from other respiratory viruses, influenza vaccination coverage, and median household income or other factors on influenza-associated excess mortality could not be examined owing to lack of specific data. Finally, the authors chose to use linear models to account for linear association between virus activity and excess mortality based on their understanding of the mechanistic link between the number of infections and the number of excess deaths (i.e., assuming that a fixed proportion of infections were fatal). Other researchers have used count-based models and these could also be an alternative approach that might lead to slightly different results.

Conclusions

The impact of influenza on excess mortality in Korea is substantial, although it varies by influenza season, age, and region. With a growing elderly population, the mortality burden of influenza will most likely increase unless more-intensive preventive measures are taken. Further studies examining the impact of influenza on medically attended illnesses and

hospitalizations, and exploring factors causing such a high degree of heterogeneity among different regions of Korea, would be beneficial in understanding the full impact of influenza on public health in Korea.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. WHO. Vaccines against influenza WHO position paper - November 2012. Wkly Epidemiol Rec. 2012; 87(47):461–476. [PubMed: 23210147]
2. WHO. [Accessed January 15, 2015] Influenza: Fact Sheets. www.who.int/mediacentre/factsheets/fs211/en/.
3. Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the U.S.: measuring disease burden and costs. Vaccine. 2007; 25(27):5086–5096. <http://dx.doi.org/10.1016/j.vaccine.2007.03.046>. [PubMed: 17544181]
4. Song JY, Cheong HJ, Choi SH, et al. Hospital-based influenza surveillance in Korea: hospital-based influenza morbidity and mortality study group. J Med Virol. 2013; 85(5):910–917. <http://dx.doi.org/10.1002/jmv.23548>. [PubMed: 23508916]
5. Chiu SS, Lau YL, Chan KH, Wong WH, Peiris JS. Influenza-related hospitalizations among children in Hong Kong. N Engl J Med. 2002; 347(26):2097–2103. <http://dx.doi.org/10.1056/NEJMoa020546>. [PubMed: 12501221]
6. Wong CM, Chan KP, Hedley AJ, Peiris JS. Influenza-associated mortality in Hong Kong. Clin Infect Dis. 2004; 39(11):1611–1617. <http://dx.doi.org/10.1086/425315>. [PubMed: 15578360]
7. Dushoff J, Plotkin JB, Viboud C, Earn DJ, Simonsen L. Mortality due to influenza in the United States--an annualized regression approach using multiple-cause mortality data. Am J Epidemiol. 2006; 163(2):181–187. <http://dx.doi.org/10.1093/aje/kwj024>. [PubMed: 16319291]
8. Thompson WW, Weintraub E, Dhankhar P, et al. Estimates of US influenza-associated deaths made using four different methods. Influenza Other Respir Viruses. 2009; 3(1):37–49. <http://dx.doi.org/10.1111/j.1750-2659.2009.00073.x>. [PubMed: 19453440]
9. Thompson WW, Moore MR, Weintraub E, et al. Estimating influenza-associated deaths in the United States. Am J Public Health. 2009; 99(Suppl 2):S225–S230. <http://dx.doi.org/10.2105/AJPH.2008.151944>. [PubMed: 19797736]
10. Muscatello DJ, Cretikos MA, Macintyre CR. All-cause mortality during first wave of pandemic (H1N1) 2009, New South Wales, Australia, 2009. Emerg Infect Dis. 2010; 16(9):1396–1402. <http://dx.doi.org/10.3201/eid1609.091723>. [PubMed: 20735923]
11. Cohen C, Simonsen L, Kang JW, et al. Elevated influenza-related excess mortality in South African elderly individuals, 1998–2005. Clin Infect Dis. 2010; 51(12):1362–1369. <http://dx.doi.org/10.1086/657314>. [PubMed: 21070141]
12. Goldstein E, Cobey S, Takahashi S, Miller JC, Lipsitch M. Predicting the epidemic sizes of influenza A/H1N1, A/H3N2, and B: a statistical method. PLoS Med. 2011; 8(7):e1001051. <http://dx.doi.org/10.1371/journal.pmed.1001051>. [PubMed: 21750666]

13. Wijngaard CC, Asten L, Koopmans MP, et al. Comparing pandemic to seasonal influenza mortality: moderate impact overall but high mortality in young children. *PLoS One*. 2012; 7(2):e31197. <http://dx.doi.org/10.1371/journal.pone.0031197>. [PubMed: 22319616]
14. Simonsen L, Spreeuwenberg P, Lustig R, et al. Global mortality estimates for the 2009 Influenza Pandemic from the GLaMOR project: a modeling study. *PLoS Med*. 2013; 10(11):e1001558. <http://dx.doi.org/10.1371/journal.pmed.1001558>. [PubMed: 24302890]
15. Warren-Gash C, Bhaskaran K, Hayward A, et al. Circulating Influenza Virus, Climatic Factors, and Acute Myocardial Infarction: A Time Series Study in England and Wales and Hong Kong. *J Infect Dis*. 2011; 203(12):1710–1718. <http://dx.doi.org/10.1093/infdis/jir171>. [PubMed: 21606529]
16. Goldstein E, Viboud C, Charu V, Lipsitch M. Improving the estimation of influenza-related mortality over a seasonal baseline. *Epidemiology*. 2012; 23(6):829–838. <http://dx.doi.org/10.1097/EDE.0b013e31826c2dda>. [PubMed: 22992574]
17. Wu P, Goldstein E, Ho LM, et al. Excess mortality associated with influenza A and B virus in Hong Kong, 1998–2009. *J Infect Dis*. 2012; 206(12):1862–1871. <http://dx.doi.org/10.1093/infdis/jis628>. [PubMed: 23045622]
18. Charu V, Chowell G, Palacio Mejia LS, et al. Mortality burden of the A/H1N1 pandemic in Mexico: a comparison of deaths and years of life lost to seasonal influenza. *Clin Infect Dis*. 2011; 53(10):985–993. <http://dx.doi.org/10.1093/cid/cir644>. [PubMed: 21976464]
19. Lemaitre M, Carrat F, Rey G, Miller M, Simonsen L, Viboud C. Mortality burden of the 2009 A/H1N1 influenza pandemic in France: comparison to seasonal influenza and the A/H3N2 pandemic. *PLoS One*. 2012; 7(9):e45051. <http://dx.doi.org/10.1371/journal.pone.0045051>. [PubMed: 23028756]
20. Freitas FT, Souza LR, Azziz-Baumgartner E, et al. Influenza-associated excess mortality in southern Brazil, 1980–2008. *Epidemiol Infect*. 2013; 141(8):1731–1740. <http://dx.doi.org/10.1017/S0950268812002221>. [PubMed: 23040669]
21. Nunes B, Viboud C, Machado A, et al. Excess mortality associated with influenza epidemics in Portugal, 1980 to 2004. *PLoS One*. 2011; 6(6):e20661. <http://dx.doi.org/10.1371/journal.pone.0020661>. [PubMed: 21713040]
22. Nielsen J, Mazick A, Glismann S, Molbak K. Excess mortality related to seasonal influenza and extreme temperatures in Denmark, 1994–2010. *BMC Infect Dis*. 2011; 11:350. <http://dx.doi.org/10.1186/1471-2334-11-350>. [PubMed: 22176601]
23. Feng L, Shay DK, Jiang Y, et al. Influenza-associated mortality in temperate and subtropical Chinese cities, 2003–2008. *Bull World Health Organ*. 2012; 90(4):279–288b. <http://dx.doi.org/10.2471/BLT.11.096958>. [PubMed: 22511824]
24. Yang L, Ma S, Chen PY, et al. Influenza associated mortality in the subtropics and tropics: results from three Asian cities. *Vaccine*. 2011; 29(48):8909–8914. <http://dx.doi.org/10.1016/j.vaccine.2011.09.071>. [PubMed: 21959328]
25. Kessaram T, Stanley J, Baker MG. Estimating influenza-associated mortality in New Zealand from 1990 to 2008. *Influenza Other Respir Viruses*. 2015; 9(1):14–19. <http://dx.doi.org/10.1111/irv.12292>. [PubMed: 25346370]
26. Korean Statistical Information Service (KOSIS). Statistical Database. Korea Statistics.
27. Mallia P, Johnston SL. Influenza infection and COPD. *Int J Chron Obstruct Pulmon Dis*. 2007; 2(1):55–64. <http://dx.doi.org/10.2147/copd.2007.2.1.55>. [PubMed: 18044066]
28. Reichert TA, Simonsen L, Sharma A, Pardo SA, Fedson DS, Miller MA. Influenza and the winter increase in mortality in the United States, 1959–1999. *Am J Epidemiol*. 2004; 160(5):492–502. <http://dx.doi.org/10.1093/aje/kwh227>. [PubMed: 15321847]
29. Nicoll A, Ciancio BC, Lopez Chavarrias V, et al. Influenza-related deaths--available methods for estimating numbers and detecting patterns for seasonal and pandemic influenza in Europe. *Euro Surveill*. 2012; 17(18)
30. Korea Centers for Disease Control and Prevention (KCDC). Influenza Weekly/Annual Report. www.cdc.go.kr/CDC/info/CdcKrInfo0402.jsp?menuIds=HOME001-MNU1132-MNU1138-MNU0045.

31. Korea Centers for Disease Control and Prevention (KCDC). Disease Web Statistics System: Weekly ILI Rate. <http://is.cdc.go.kr/dstat/jsp/stat/stat0101.jsp>.
32. Korea Meteorological Administration (KMA). Archive of daily weather. www.kma.go.kr/weather/climate/past_table.jsp.
33. Shaman J, Kohn M. Absolute humidity modulates influenza survival, transmission, and seasonality. *Proc Natl Acad Sci U S A*. 2009; 106(9):3243–3248. <http://dx.doi.org/10.1073/pnas.0806852106>. [PubMed: 19204283]
34. Barreca AI, Shimshack JP. Absolute humidity, temperature, and influenza mortality: 30 years of county-level evidence from the United States. *Am J Epidemiol*. 2012; 176(Suppl 7):S114–S122. <http://dx.doi.org/10.1093/aje/kws259>. [PubMed: 23035135]
35. Frank AL, Taber LH, Wells JM. Comparison of infection rates and severity of illness for influenza A subtypes H1N1 and H3N2. *J Infect Dis*. 1985; 151(1):73–80. <http://dx.doi.org/10.1093/infdis/151.1.73>. [PubMed: 3965595]
36. CDC U. Estimates of deaths associated with seasonal influenza --- United States, 1976–2007. *MMWR Morb Mortal Wkly Rep*. 2010; 59(33):1057–1062. [PubMed: 20798667]
37. Korea Centers for Disease Control and Prevention (KCDC). Analysis of reported pandemic influenza (A/H1N1 2009) virus infections in Korea. KCDC; 2010.
38. Kim JH, Yoo HS, Lee JS, et al. The spread of pandemic H1N1 2009 by age and region and the comparison among monitoring tools. *J Korean Med Sci*. 2010; 25(7):1109–1112. <http://dx.doi.org/10.3346/jkms.2010.25.7.1109>. [PubMed: 20592911]
39. Korea Centers for Disease Control and Prevention (KCDC). 2009–2010 Influenza A(H1N1) vaccination program in Korea. KCDC; 2010.
40. Viboud C, Miller M, Olson D, Osterholm M, Simonsen L. Preliminary Estimates of Mortality and Years of Life Lost Associated with the 2009 A/H1N1 Pandemic in the U.S. and Comparison with Past Influenza Seasons. *PLoS Curr*. 2010; 2:RRN1153. <http://dx.doi.org/10.1371/currents.RRN1153>. [PubMed: 20352125]
41. Lozano, R.; Murray, CJL.; Lopez, AD.; Satoh, T. Miscoding and misclassification of ischaemic heart disease mortality. WHO; 2001.
42. Jougl E, Papoz L, Balkau B, Maguin P, Hatton F. Death certificate coding practices related to diabetes in European countries--the 'EURODIAB Subarea C' Study. *Int J Epidemiol*. 1992; 21(2): 343–351. <http://dx.doi.org/10.1093/ije/21.2.343>. [PubMed: 1428491]
43. Noymer A, Nguyen AM. Influenza as a proportion of pneumonia mortality: United States, 1959–2009. *Biodemography Soc Biol*. 2013; 59(2):178–190. <http://dx.doi.org/10.1080/19485565.2013.833816>. [PubMed: 24215258]
44. Korea Centers for Disease Control and Prevention (KCDC). Influenza Management Guideline (2013–2014). 2013
45. Organisation for Economic Co-operation and Development (OECD). OECD StatExtracts: Health Status. http://stats.oecd.org/index.aspx?DataSetCode=HEALTH_STAT.

Figure 1. Annual influenza-associated excess mortality rates and proportions of all-cause mortality attributable to influenza in 16 cities and provinces in Korea from 2003 through 2013.

Table 1
Type and Subtype-Specific Excess Mortality Rates in Korea (per 100,000 Persons)

Season ^a	Duration	Predominant strain(s)	A(sH1N1)	(95% CI)	A(sH3N2)	(95% CI)	B	(95% CI)	A(pH1N1)	(95% CI)	All flu	(95% CI)
03-04	Spring	5 weeks	A(sH3N2)	0.00	(0.00, 0.00)	3.04	(2.45, 3.62)	1.42	(0.78, 2.05)	--	4.46	(3.56, 5.29)
04-05	--	--		0.06	(0.01, 0.12)	3.81	(3.06, 4.52)	0.63	(0.35, 0.90)	--	4.50	(3.61, 5.24)
05-06	Winter	3 weeks	A(sH1N1)	1.29	(0.22, 2.39)	1.45	(1.16, 1.72)	0.62	(0.35, 0.90)	--	3.36	(2.26, 4.49)
06-07	Winter	3 weeks	A(sH3N2)	0.49	(0.08, 0.90)	5.68	(4.57, 6.74)	0.45	(0.25, 0.65)	--	6.62	(5.32, 7.80)
07-08	Winter Spring	19 weeks	A(sH1N1), BB, A(sH3N2)	0.68	(0.11, 1.26)	1.85	(1.49, 2.20)	3.32	(1.84, 4.80)	--	5.85	(4.10, 7.36)
08-09	Winter Spring	10 weeks 14 weeks	A(sH1N1) A(sH3N2)	2.06	(0.34, 3.80)	3.70	(2.98, 4.39)	0.02	(-0.01, 0.05)	--	5.78	(3.98, 7.72)
09-10	Winter Spring	40 weeks	A(pH1N1) B	--	--	0.03	(0.03, 0.04)	0.85	(-1.29, 2.96)	1.16	2.04	(-1.75, 6.29)
10-11	Winter	25 weeks	A(pH1N1)	--	--	2.02	(1.62, 2.40)	0.02	(0.01, 0.03)	0.90	2.94	(0.99, 4.85)
11-12	Winter Spring	19 weeks	A(sH3N2) B	--	--	11.85	(9.53, 14.08)	6.90	(3.82, 9.98)	0.00	18.76	(14.69, 22.49)
12-13	Winter Spring	15 weeks	A(sH3N2)	--	--	4.84	(3.89, 5.75)	0.16	(0.09, 0.23)	0.13	5.13	(4.12, 6.07)

^a 03-04 through 06-07: Weekly ILI rate >7.5 per 1,000 persons
 07-08: Weekly ILI rate >3 per 1,000 persons
 08-09 through 09-10: Weekly ILI rate > 2.6 per 1,000 persons
 10-11: Weekly ILI rate >2.9 per 1,000 persons
 11-12: Weekly ILI rate >3.8 per 1,000 persons
 12-13: Weekly ILI rate >4.0 per 1,000 persons

Table 2
Average Type and Subtype-Specific Annual Excess All-Cause Mortality Rates in Korea, 2003–2013 (per 100,000 Persons Each Year)

Type	0–4 y	95% CI	5–14 y	95% CI	15–44 y	95% CI	45–64 y	95% CI	65 y	95% CI	All- ages	95% CI
A(sH1N1)	0.07	(−0.34, 0.41)	0.06	(−0.11, 0.22)	−0.03	(−0.26, 0.25)	0.79	(0.28, 1.36)	5.33	(0.40, 9.80)	0.76	(0.15, 1.44)
A(sH3N2)	0.12	(−0.35, 0.46)	0.07	(−0.11, 0.24)	0.11	(−0.18, 0.38)	1.11	(0.31, 1.71)	31.94	(25.43, 37.06)	3.84	(3.17, 4.60)
B	0.37	(0.02, 0.66)	0.11	(−0.04, 0.23)	0.32	(0.09, 0.59)	0.83	(0.19, 1.29)	10.75	(4.41, 15.30)	1.45	(0.78, 2.07)
A(αH1N1)	−0.51	(−1.03, 0.03)	0.04	(−0.16, 0.24)	0.05	(−0.39, 0.39)	0.79	(−0.13, 1.73)	2.73	(−5.02, 10.15)	0.55	(−0.49, 1.69)
All Flu	0.32	(−0.43, 0.87)	0.23	(−0.12, 0.52)	0.44	(−0.05, 0.87)	2.73	(1.60, 3.65)	46.98	(36.40, 55.82)	5.97	(4.89, 7.19)

Table 3
Average Cause-Specific Excess Mortality Rates in Different Age Groups, 2003–2013 (per 100,000 Persons Each Year)

	Average excess mortality rate (per 100,000 persons)										All-ages	(95% CI)
	0–4 y	(95% CI)	5–14 y	(95% CI)	15–44 y	(95% CI)	45–64 y	(95% CI)	65 y	(95% CI)		
Respiratory diseases	0.17	(0.03, 0.34)	0.02	(0.00, 0.05)	0.05	(0.03, 0.08)	0.37	(0.30, 0.55)	11.45	(10.05, 14.28)	1.34	(1.21, 1.66)
Pneumonia & Influenza	0.08	(0.00, 0.18)	0.00	(−0.01, 0.02)	0.05	(0.03, 0.07)	0.22	(0.17, 0.30)	5.49	(5.05, 7.14)	0.68	(0.63, 0.96)
Chronic lower respiratory disease	0.02	(−0.02, 0.06)	0.01	(0.00, 0.02)	0.00	(−0.01, 0.01)	0.14	(0.09, 0.25)	5.63	(4.65, 7.18)	0.62	(0.53, 0.78)
Cardiovascular diseases	−0.02	(−0.13, 0.09)	0.02	(−0.02, 0.06)	0.12	(0.04, 0.21)	0.83	(0.44, 1.22)	10.60	(8.09, 13.86)	1.41	(1.14, 1.80)
Heart disease	−0.05	(−0.14, 0.05)	0.01	(−0.01, 0.05)	0.08	(0.04, 0.15)	0.51	(0.28, 0.80)	5.60	(4.18, 7.48)	0.75	(0.61, 0.98)
Cerebrovascular disease	0.04	(−0.01, 0.08)	−0.01	(−0.03, 0.03)	0.03	(−0.02, 0.08)	0.27	(0.01, 0.51)	3.90	(1.69, 5.74)	0.60	(0.40, 0.81)
Malignant neoplasm	0.08	(−0.05, 0.22)	0.00	(−0.08, 0.07)	0.07	(−0.02, 0.19)	0.13	(−0.29, 0.62)	3.76	(1.55, 5.52)	0.49	(0.24, 0.73)
Diabetes mellitus	0.00	(0.00, 0.01)	0.00	(−0.01, 0.01)	0.03	(0.01, 0.07)	0.32	(0.15, 0.53)	3.38	(2.55, 4.55)	0.46	(0.37, 0.60)
Renal disease	0.02	(0.00, 0.06)	0.00	(−0.01, 0.01)	−0.01	(−0.03, 0.01)	0.02	(−0.07, 0.13)	0.63	(0.24, 1.06)	0.07	(0.02, 0.13)
Chronic liver disease	0.00	(−0.01, 0.01)	0.00	(0.00, 0.00)	−0.02	(−0.07, 0.05)	0.39	(0.12, 0.66)	0.25	(−0.16, 0.71)	0.12	(0.04, 0.20)
Degenerative disease of nervous system	0.00	(−0.03, 0.02)	0.00	(0.00, 0.01)	0.00	(0.00, 0.00)	0.00	(−0.03, 0.02)	1.73	(1.40, 2.34)	0.19	(0.15, 0.28)
7 Major causes	0.25	(0.01, 0.53)	0.05	(−0.04, 0.14)	0.24	(0.09, 0.41)	1.76	(0.96, 2.52)	32.60	(28.47, 39.79)	4.16	(3.76, 5.08)
Other causes	0.06	(−0.67, 0.62)	0.21	(−0.04, 0.47)	0.20	(−0.30, 0.69)	0.77	(0.08, 1.33)	14.31	(10.33, 20.28)	1.81	(1.15, 2.64)
All causes	0.32	(−0.41, 0.96)	0.23	(−0.09, 0.50)	0.44	(−0.03, 0.94)	2.73	(1.58, 3.87)	46.98	(38.32, 58.94)	5.97	(4.96, 7.59)
Traffic accident (Control)	−0.07	(−0.24, 0.08)	0.01	(−0.07, 0.08)	−0.11	(−0.22, −0.04)	−0.08	(−0.34, 0.06)	−0.13	(−0.81, 0.29)	−0.08	(−0.22, −0.01)