Supply of neuraminidase inhibitors related to reduced influenza A (H1N1) mortality during the 2009–2010 H1N1 pandemic: summary of an ecological study

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When the influenza A (H1N1) pandemic spread across the globe from April 2009 to August 2010, many WHO Member States used antiviral drugs, specifically neuraminidase inhibitors (NAIs) oseltamivir and zanamivir, to treat influenza patients in critical condition. Antivirals have been found to be effective in reducing severity and duration of influenza illness, and likely reduce morbidity; however, it is unclear whether NAIs used during the pandemic reduced H1N1 mortality. To assess the association between antivirals and influenza mortality, at an ecologic level, country-level data on supply of oseltamivir and zanamivir were compared to laboratory-confirmed H1N1 deaths (per 100 000 people) from July 2009 to August 2010 in 42 WHO Member States. From this analysis, it was found that each 10% increase in kilograms of oseltamivir, per 100 000 people, was associated with a 1.6% reduction in H1N1 mortality over the pandemic period [relative rate (RR) = 0.84 per log increase in oseltamivir supply]. Each 10% increase in kilogram of active zanamivir, per 100 000, was associated with a 0.3% reduction in H1N1 mortality (RR = 0.97 per log increase). While limitations exist in the inference that can be drawn from an ecologic evaluation, this analysis offers evidence of a protective relationship between antiviral drug supply and influenza mortality and supports a role for influenza antiviral use in future pandemics. This article summarises the original study described previously, which can be accessed through the following citation: Miller PE, Rambachan A, Hubbard RJ, Li J, Meyer AE, et al. (2012) Supply of Neuraminidase Inhibitors Related to Reduced Influenza A (H1N1) Mortality during the 2009–2010 H1N1 Pandemic: An Ecological Study. PLoS ONE 7(9): e43491.

Keywords Antivirals, epidemiology, global health, influenza.

Introduction

Antivirals, and specifically neuraminidase inhibitors (NAIs) including oseltamivir and zanamivir, are efficacious in lowering influenza-related morbidity, reducing both the duration of symptoms of influenza and the overall severity of the illness, along with reducing the overall disease attack rate and lessening the scope of local epidemics.1–7 These results prompted international recommendations for the use of NAIs during the 2009 H1N1 influenza pandemic. Various observational studies have provided evidence of improved survival with prompt antiviral treatment within 48 hours of influenza symptom onset, however not all studies have found this clear benefit.8–11 The purpose of this ecological analysis was, therefore, to examine the relationship of mortality specific to pandemic H1N1 influenza and NAI supply at the level of WHO Member States and provide further evidence of the aggregate role that NAIs may play in reducing influenza mortality in future pandemics. While group-level analyses cannot indicate the efficacy or effectiveness of NAIs on individual-level risk of fatal influenza, they can inform policy makers and community leaders of the impact of an aggregate policy, such as supply of or investment in antivirals, on overall mortality trends during a pandemic.

Methods

Data for total kilograms of NAIs distributed and laboratory-confirmed deaths attributed to pandemic H1N1 from July 2009 to August 2010 were available for 62 WHO Member States in all WHO regions. Data on weekly mortality of
laboratory-confirmed pandemic H1N1 influenza were obtained from the WHO and were summed over the entire pandemic period. Data on country-level NAI supply, in kilograms, were collected by Intercontinental Medical Statistics. Total population estimates, derived from the United Nations Statistics Division, were included to estimate the mortality and NAI supply per 100 000 people. Additional Member State-level data on possible confounding factors were compiled from United Nations and other international agencies. Health indicators, health-related indicators and socio-economic indicators were considered for possible confounding (Table 1).

Member states were excluded from the model if there were insufficient data available on potential confounding factors, leaving 42 Member States available for inclusion in the primary analysis (Figure 1).

Poisson regression was used to model H1N1 mortality rates during the 14-month period using the combined supply of oseltamivir and zanamivir. Parameters, including the NAI supply, were log transformed for the model if they were found to be roughly non-normally distributed. The final model considered pregnancy rate, life expectancy, hospital bed density, per capita health spending, percentage of the population over 65 years old, under-five mortality rate, adult literacy rate, the rate of male obesity and physician density along with NAI supply per 100 000. The statistical program R (http://www.r-project.org/) was used for all analysis and P-values ≤ 0.05 were considered statistically significant.

| Table 1. Health, health-related and socio-economic indicators (references noted) |
|---------------------------------|---------------------------------|
| Health indicators              |                                |
| Under 5 mortality (per 1000)   | [15]                            |
| % of Adult Population with HIV | [16,17]                         |
| Life Expectancy (male, female, overall) | [18]                              |
| Obesity Rate as body mass index >30 (male, female) | [17,19] |
| % of Population with Improved Sanitation Quality | [17] |
| % Population with Water Quality Standards | [17] |
| Environmental Workers (per 10 000) | [20] |
| Community Health Workers (per 10 000) | [20] |
| Government Health Spending per Capita | [20] |
| Private Health Spending per Capita | [20] |
| Total Per Capita Health Spending | [20] |
| % of Infant Population with Hepatitis B Vaccination | [15] |
| Physician Density (per 10 000) | [20] |
| Hospital Beds (per 10 000) | [20] |
| Pregnancy Rate (per 1000) | [21] |
| % Population >65 years | [21] |
| Adult Literacy Rate | [17] |
| % Population in Urban Areas | [17] |
| Measure of Political Stability | [22] |
| Per Capita Gross Domestic Product | [17] |
| Population Density | [17] |

**Results**

From July 2009 to August 2010, the median total H1N1-specific mortality rate was 0.65 per 100 000 people among the 42 Member States (IQR: 0.40–1.05 per 100 000 people). The median total oseltamivir supply over the pandemic period was 0.24 kg of active drug per 100 000 people (IQR: 0.042–0.66), or roughly 1600 adult doses per 100 000. For zanamivir, the median supply over the pandemic was much lower at 0.01 kg per million people (IQR: 0.0009–0.05), or roughly 200 adult doses per million. The highest NAI supply rates were seen in the European and Western Pacific Member states, whereas Member States in the Americas and in the Eastern Mediterranean had the lowest total supplies (Table 2).

After adjusting for potential confounders, a 10% increase in kilograms of oseltamivir per 100 000 people was associated with a 1.6% decrease in H1N1 mortality rate (95% CI: 1.5–1.7% reduction), and a 10% increase in kilograms of zanamivir per 100 000 was associated with a 0.3% decrease in mortality rate (95% CI: 0.2–0.4% reduction).

**Discussion**

Evidence from individual-level observational studies varies on the effect of antivirals on reducing influenza mortality. The results of this analysis suggest that, after controlling for various differences between Member States, higher supplies of oseltamivir and zanamivir were significantly associated with reductions in H1N1 mortality from July 2009 to August 2010, namely each 10% increase in kilograms of oseltamivir and zanamivir supply, per 100 000 people, was associated with 1.6% and 0.3% mortality reductions, respectively.

Differences between WHO Member States, including socio-demographic, economic and healthcare infrastructure could confound the ecologic associations found in this analysis. While every attempt was made to adjust for differences, several important confounders such as air quality or land use patterns – which may impact a population’s susceptibility to influenza or exposure to infected livestock – may continue to bias the estimated main effect. Additionally, as in any ecologic analysis, these associations may not be reflective of the individual-level association, and evidence from controlled studies is needed to evaluate the possibility of a causal relationship between NAI treatment and influenza mortality.

Our analysis appears to be robust to several uncertain aspects of the included data. For example, restricting the analysis to Member States with a high degree of laboratory testing capacity or augmenting the drug supply to account for underestimation of the full pharmaceutical market resulted in no substantive change in the estimated effect of NAI supply on H1N1-specific mortality.
Several other limitations exist that may impact the validity of our results. First, the results of this analysis depend on the assumption that the supply of NAIs reflects the total NAIs administered by each Member State. If large quantities of NAIs were purchased and not distributed, or distributed but not administered during the pandemic period, the observed association may underestimate the true effect that NAIs have on influenza replication and subsequent influenza mortality.

Finally, only 42 Member States, drawn from five of the six WHO Regions, had available data for inclusion in the analysis. As a consequence, 26 included Member States are located in the European Region, and no Member States from the African Region were included, thus limiting the scope and generalizability of the findings.

Treatment of symptomatic influenza with NAIs is only one tool in a toolbox of interventions that can limit transmission, morbidity and mortality from influenza. Antiviral treatment needs to be combined with vaccination, case isolation, school or workplace closure and travel restriction efforts to have the greatest impact on reducing

Table 2. Median total and monthly estimates of influenza A (H1N1) mortality and kilograms of oseltamivir and zanamivir by World Health Organization region

| Member states included | The Americas (AMRO) | China (SEARO) | Europe (EURO) | Eastern Mediterranean (EMRO) | Western Pacific (WPRO) |
|------------------------|-------------------|---------------|---------------|-----------------------------|-----------------------|
| Mortality (H1N1 deaths per 100 000 people) | 6 | 1 | 26 | 5 | 4 |
| Total median | 1-18 | 0-18 | 0-63 | 0-37 | 0-51 |
| IQR | 1-08–1-33 | – | 0-45–0-87 | 0-15–0-56 | 0-13–0-89 |
| Monthly median | 0-084 | 0-013 (-) | 0-045 | 0-027 | 0-037 |
| IQR | 0-077–0-095 | – | 0-032–0-062 | 0-010–0-040 | 0-0096–0-064 |
| Oseltamivir (kg per 100 000 people) | | | | | |
| Total median | 0-14 | 0-00013 | 0-47 | 0-017 | 0-46 |
| IQR | 0-032–0-46 | – | 0-12–0-72 | 0-013–0-57 | 0-29–1-52 |
| Monthly Median | 0-0097 | 0-000094 | 0-034 | 0-0012 | 0-033 |
| IQR | 0-0023–0-033 | – | 0-0087–0-052 | 0-00090–0-040 | 0-020–0-11 |
| Zanamivir (kg per 1 million people) | | | | | |
| Total median | 0-0034 | 0-0002 | 0-0091 | 0-024 | 0-026 |
| IQR | 0-00016–0-031 | – | 0-0010–0-064 | 0-017–0-037 | 0-015–1-2 |
| Monthly median | 0-00024 | 0-000014 | 0-00065 | 0-0017 | 0-0018 |
| IQR | 0-000012–0-0022 | – | 0-000072–0-0046 | 0-0012–0-0026 | 0-0011–0-085 |
the extent of a local epidemic or global pandemic. The NAI supply, used in this analysis, is likely correlated with overall influenza pandemic preparedness activities conducted in the included Member States, potentially biasing the estimated effect of NAIs. Of note, however, pharmaceutical interventions, including NAI supply, most likely played a greater role in reducing mortality.

Limitations aside, this analysis demonstrates an association between NAI supply and H1N1 mortality during the 2009 influenza pandemic at an ecological level consistent with other findings on the individual level. This effect does not seem large on a population level and equates to a drop in mortality in the Americas from the observed 1.18 per 100 000 to 1.16 per 100 000 for a 10% increase kg of oseltamivir/100 000. However, the observed range of supplies of oseltamivir was quite large, and in the Americas, our model predicted that the mortality reduction between Member States with drug supply at the level of the 25th percentile (0.032 kg/100 000) compared with the 75th percentile (0.46 kg/100 000) would, on average, be 37% (95% CI: 35–39% reduction). Thus, changes in drug supply on a larger scale may lead to significant declines in influenza-related mortality when used appropriately. Our analysis suggests the importance placed on efforts to treat influenza and may help policy makers and public health officials plan for future influenza pandemics.

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Conflict of interest

Co-author, PS, is employed by IMS Health. IMS Health is paid by the pharmaceutical industry and governments around the world to collect, analyze, and/or consult on patterns relating to the consumption of medicines, including the manufacturers of the two medicines described in this study. No payments to IMS Health or PS were made for this analysis.

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