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Air Travel and the Spread of Influenza: Important Caveats

Cécile Viboud, Mark A. Miller, Bryan T. Grenfell, Ottar N. Bjørnstad, Lone Simonsen

While air travel contributes to the spread of influenza epidemics, the magnitude of impact is not clear compared to other factors—a crucial issue when considering a flight ban in the context of pandemic planning. Recent modeling efforts simulating the spread of pandemic influenza have concluded that such an intervention would matter little relative to other interventions [1–3]. But this assessment has now been challenged by an observational study of influenza in the winter following the post-9/11/2001 depression in air traffic. Brownstein and colleagues' study published in the September issue of *PLoS Medicine* [4] correlates variations in air traffic volume with patterns of timing and spread in influenza epidemics, based on United States mortality data from nine epidemic seasons between 1996 and 2005. While we find the study interesting, we have identified several important caveats and question the robustness of the conclusions.

The core of this study's results lies in the observation that the 2001–2002 influenza epidemic immediately following 9/11 was late in the season and peaked in March (week of year 11), whereas the eight surrounding epidemics peaked between the end of December and the end of February (week of year 52 to 9). The authors attribute this delay to the 27% decline in air traffic that followed 9/11.

Given the complexities of influenza virus subtype cycling and antigenic drift [5,6], it is essential to consider longer-term disease data spanning much more than nine years to interpret the “lateness” of the 2001–2002 epidemic. Using US national vital statistics data covering 30 winters from 1972 to 2002 [5], we identified four epidemics peaking in the month of March (13%), including the 2001–2002 epidemic following 9/11, but also two epidemics in the 1970s and the more recent 1991–1992 epidemic (Figure 1A). Furthermore, the average timing of influenza epidemics has not changed between 1972 and 2002—despite a concurrent and steady increase in air traffic volume by over 300% (Figure 1A) [7]. Indeed, during the earlier part of the last century when air traffic was minimal, influenza epidemics rapidly circulated around the world. Moreover, real-time influenza virus surveillance data from the US Centers for Disease Control and Prevention [8] show that last winter's (2005–2006) epidemic was even more delayed than the epidemic following 9/11, despite a 20% increase in air passenger traffic compared to the situation before 9/11 [7]. Clearly, late-season influenza epidemics have occurred and are still occurring even in the absence of restrictions on air travel. Hence a longer time perspective, with observations from both prior and more recent data, challenges this study's conclusions.

In addition to comparing the timing of influenza epidemics across different seasons, Brownstein et al. analyzed the rate of disease spread among US administrative regions for their nine seasons of interest (1996–2005). In our previous work, we estimated the rate of influenza spread among all US states for 30 consecutive seasons (1972–2002) [5]. Our analysis shows that the epidemic following 9/11 spread at

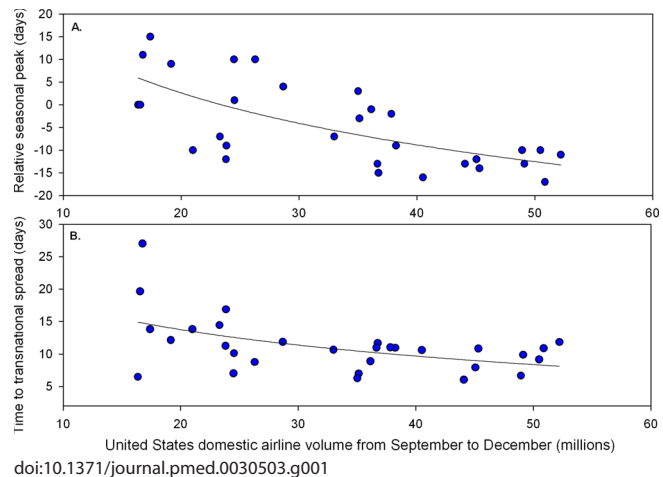


Figure 1. Patterns of Timing (A) and Spread (B) of 30 Influenza Epidemics in the US, Together with Trends in Air Travel Statistics. Influenza patterns are based on weekly national vital statistics from 1972 to 2002 [5]. Air travel statistics represent the annual number of domestic and international passengers on US air carriers (scheduled flights, secondary y-axis) [7]. (A) Time series of timing of national peaks of influenza mortality. The 2001–2002 epidemic following 9/11 peaked in March, and so did two epidemics in the 1970s and one in the 1990s. (B) Time series of rate of spread between US states. The rate of spread of the 2001–2002 epidemic following 9/11 is comparable to that of other epidemics. Rate of spread as calculated in [5], based on the timing of epidemic peaks in each state.

a rate comparable to other epidemics (Figure 1B), even after adjusting for the subtype of circulating viruses [5]. To increase our understanding of the spread of influenza, it is essential to quantify the relative importance of different modes of transportation. As an example, our recent study considered multiple modes of transportation (including air travel) and identified travel to and from work as a key determinant of the regional spread of epidemics [5].

In conclusion, Brownstein and colleagues' analysis of the “natural experiment” of the post-9/11 season is innovative and ingenious—but in and of itself could not demonstrate a robust association or a causal link between the decrease in air traffic and delayed timing of influenza epidemics. Even if there in fact had been a delay as hypothesized, the study lacked power to address the hypothesis, because this single “natural experiment” was set in a background of considerable variability in influenza epidemic patterns. Extrapolations from the study's findings predict that a flight ban could delay a pandemic by two months [9]—but we have shown here that this prediction is not supported by the analysis of more extensive disease data and transportation statistics. It is also unclear how a “natural experiment” conducted in the inter-pandemic period is applicable to a pandemic situation, where novel influenza viruses have higher transmissibility and circulate in fully susceptible populations, and may cause different age-patterns of transmission [10]. While Brownstein and colleagues' study represents an intriguing starting point, this study alone does not provide the critical quantitative evidence needed to evaluate the impact of travel restrictions on future pandemics. ■

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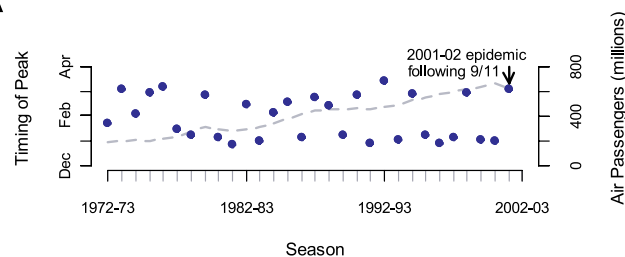
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Air Travel and the Spread of Influenza: Authors' Reply

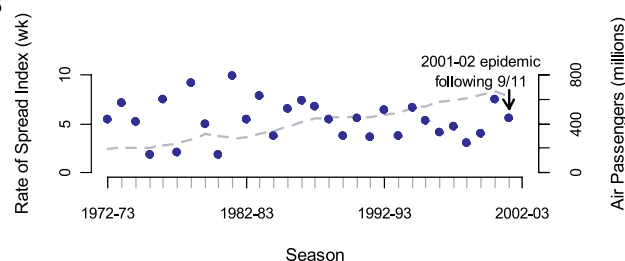
Viboud et al. [1] offer thoughtful commentary on our paper [2], opening a scientific exchange that we hope brings attention to a critical issue. We reported the first empirical and quantitative evidence for the effect of airline travel on the rate of epidemic influenza spread. Though other investigators have also found this relationship [3–6], there is no consensus on effect size. We welcome scrutiny of our methods and results and believe the findings stand for the following reasons.

Viboud et al., taking a longer historical perspective, suggest that the slower spread and late peaking of the 2001–2002 season is not unique and highlight three other late seasons dominated by influenza B (1992–1993, 1973–1974, and 1976–1977). Recent studies, including one by Viboud and colleagues, find that B seasons have different epidemiological characteristics than A/H3N2 seasons, which may explain the late peaking in these years [7,8]. As 2001–2002 was

A



B



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Figure 1. Influence of United States Airline Volume on Influenza Spread and the Timing of Yearly Transmission over 30 Influenza Seasons

(A) The association between airline travel from September to December and the timing of the US influenza peak is displayed. Airline volume significantly predicts the timing of seasonal influenza mortality ($r^2 = 0.460$; $p < 0.001$). The timing of seasonal national influenza mortality (blue dots) is estimated from cross-correlation of each season with the 1972–1973 season. (B) The association between airline travel from September to December and time to transnational US spread is displayed. The numbers of traveling domestic passengers significantly predicts transnational influenza spread ($r^2 = 0.265$; $p = 0.004$). Index spread of influenza (blue dots) is estimated from the 99% confidence interval of the cross-correlation values for the nine major geographic regions of the United States against the national curve for a given year, as previously described [2].

dominated by influenza A/H3N2, late peaking in 2001–2002 cannot be explained by dominant subtype (nor climatic conditions). Our study period from 1996–2005 represents the longest stretch of A/H3N2 seasons in over 30 years, essentially controlling for subtype. Viboud et al. also point to the 2005–2006 season as particularly delayed. We examined peaking during that season using mortality data from the US Centers for Disease Control and Prevention, in order to compare to our estimates from prior seasons [9]. We find that mortality as well as morbidity was bimodal, with larger peaks in January and December, respectively. We thus reaffirm that 2001–2002, being the latest peaking H3N2 season in over 30 years, is an aberrant season for which airline travel interruption remains the best explanation.

Viboud and colleagues' letter does not take into account that our results are not simply based on an outlier year, nor are they based on a single data source. Rather, we have revealed an important correlation across nine influenza seasons. The impact of airline volume on flu spread does not depend on the 2001–2002 season and remains significant even after its exclusion. Since considering longer time series may provide insight, we repeated our methods on the 30-year mortality time series which Viboud et al. also analyzed [10]. We employed the same spatial aggregation (nine geographic regions) and time series methods as described in [2]. We

found substantial long-term log-linear trends toward earlier peaking and faster spreading influenza epidemics that are correlated with air travel volume ($r^2 = 0.460$; $p < 0.001$ and $r^2 = 0.265$; $p = 0.004$, respectively, Figure 1). Thus, our new analyses of longer-term data support an effect of airline travel volume.

We strongly caution that other factors may influence these trends, including population density, air passenger demographics, ground transportation, and climate. Our design relies on a shorter, more recent time series to avoid confounding by longer term secular trends that may be evident in the 30-year time series. Given the three year backlog of the 30-year dataset, the data Viboud et al. use do not permit the interrupted time series analysis at the core of our investigation.

Reconciliation of our different time series methodologies and datasets should be considered in future research. Nonetheless, because our results were confirmed with viral surveillance data, we remain confident in the robustness of our analysis. We agree that other modes of transportation are important influences; our paper makes no claim that air travel is the only mechanism of spread, and we explicitly report that our model explains a portion of the variation in yearly influenza spread and peak.

Finally, Viboud et al. emphasize the limited applicability of our findings to pandemics. We agree and have highlighted this limitation in our paper. The decision to restrict travel should be multifactorial. We do hope that it will be evidence based. Our analyses (including those presented here) provide empirical insight into the previously uncharacterized effect of air travel fluctuation on influenza spread. They are one contribution to a small body of investigations that are forming the basis of global policy on flu preparedness. Though the effect we observe might be smaller under pandemic conditions, the benefit of a delay is worthy of consideration by scientists and policy makers where lives are at stake and even a short lead time may be of enormous public health value.

We are pleased that Viboud et al. have engaged in a discourse that we hope will strengthen the scientific basis of pandemic preparedness. We call on governments, industry, and health care to create a more accessible, freely available, and well-documented data repository for geographically and temporally detailed data on influenza [11] and encourage empirical analyses of the dynamics and mechanisms of influenza spread. ■

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Fluoxetine and Suicide Rates: Suicide and the Economy

Carlos A. Camargo, Daniel A. Bloch

We wish to comment on the paper by Milane et al. [1] and also refer to the Perspective by Baune and Hay [2] in the June issue of *PLoS Medicine* on the effect of fluoxetine prescriptions on the suicide rate in the United States. Milane et al. examined two sets of variables: the number of prescriptions for fluoxetine in the United States, and the Census Bureau mortality tables with the age adjusted suicide rates for the years 1988 to 2002. The date 1988 is chosen because in that year fluoxetine was introduced in the US. The authors report that the Spearman correlation coefficient between the two sets of variables equals -0.92 with a p -value of less than 0.001. The less suicides, the more tablets of fluoxetine are prescribed, or vice versa. The least-squares regression line is displayed in Figure 1.

From this simple association they build an elaborate edifice, predicting what the suicide trends would have been had fluoxetine not been prescribed, and they calculate figures for “the thousands of lives saved” for both men and women...even though it is not known how many of these prescriptions were for men or for women, whether the patients took the tablets or not, or for how long they took the medication. In addition, the baseline period used to calculate the suicide trend, and thus to predict the future, was arbitrary: from 1960 to 1987, when the suicide rates had a slight gradual increase in the 1970s. Had they used the period 1950 to 1987, a different “trend” would have been obtained, since the suicide rates decreased during the economic expansion of the 1950s [3].

It is widely known that one cannot infer causality simply based on statistical association. Baune and Hay pointed this out and wrote: “In a study like this, it is also important to consider other potential explanations for the fall of suicide