Nonpharmaceutical Interventions Implemented by US Cities During the 1918-1919 Influenza Pandemic

Context A critical question in pandemic influenza planning is the role nonpharmaceutical interventions might play in delaying the temporal effects of a pandemic, reducing the overall and peak attack rate, and reducing the number of cumulative deaths. Such measures could potentially provide valuable time for pandemic-strain vaccine and antiviral medication production and distribution. Optimally, appropriate implementation of nonpharmaceutical interventions would decrease the burden on health care services and critical infrastructure.

Objectives To examine the implementation of nonpharmaceutical interventions for epidemic mitigation in 43 cities in the continental United States from September 8, 1918, through February 22, 1919, and to determine whether city-to-city variation in mortality was associated with the timing, duration, and combination of nonpharmaceutical interventions; altered population susceptibility associated with prior pandemic waves; age and sex distribution; and population size and density.

Design and Setting Historical archival research, and statistical and epidemiological analyses. Nonpharmaceutical interventions were grouped into 3 major categories: school closure; cancellation of public gatherings; and isolation and quarantine.

Main Outcome Measures Weekly excess death rate (EDR); time from the activation of nonpharmaceutical interventions to the first peak EDR; the first peak weekly EDR; and cumulative EDR during the entire 24-week study period.

Results There were 115,340 excess pneumonia and influenza deaths (EDR, 500/100,000 population) in the 43 cities during the 24 weeks analyzed. Every city adopted at least 1 of the 3 major categories of nonpharmaceutical interventions. School closure and public gathering bans activated concurrently represented the most common combination implemented in 34 cities (79%); this combination had a median duration of 4 weeks (range, 1-10 weeks) and was significantly associated with reductions in weekly EDR. The cities that implemented nonpharmaceutical interventions earlier had greater delays in reaching peak mortality (Spearman r = -0.74, P < .001), lower peak mortality rates (Spearman r = 0.31, P = .02), and lower total mortality (Spearman r = 0.37, P = .008). There was a statistically significant association between increased duration of nonpharmaceutical interventions and a reduced total mortality burden (Spearman r = −0.39, P = .005).

Conclusions These findings demonstrate a strong association between early, sustained, and layered application of nonpharmaceutical interventions and mitigating the consequences of the 1918-1919 influenza pandemic in the United States. In planning for future severe influenza pandemics, nonpharmaceutical interventions should be considered for inclusion as companion measures to developing effective vaccines and medications for prophylaxis and treatment.
body of theoretical modeling research suggests that nonpharmaceutical interventions might play a salubrious role in delaying the temporal effect of a pandemic; reducing the overall and peak attack rate; and reducing the number of cumulative deaths.\textsuperscript{11-13} Such measures could potentially provide valuable time for production and distribution of pandemic-strain vaccine and antiviral medication. Optimally, appropriate implementation of nonpharmaceutical interventions would decrease the burden on health care services and critical infrastructure.

The historical record of the 1918-1919 influenza pandemic in the United States constitutes one of the largest recorded experiences with the use of nonpharmaceutical interventions to mitigate an easily spread, high mortality and morbidity influenza virus strain (ie, a category 4-5 pandemic using the Centers for Disease Control and Prevention February 2007 Interim Pre-Pandemic Planning Guidance).\textsuperscript{16} Our study focused on this data set by assessing the nonpharmaceutical interventions implemented in 43 cities in the continental United States from September 8, 1918, through February 22, 1919, a period that encompasses all of the second pandemic wave (September-December 1918) and the first 2 months of the third wave (January-April 1919) and represents the principal time span of activation and deactivation of nonpharmaceutical interventions. The purpose was to determine whether city-to-city variation in mortality was associated with the timing, duration, and combination (or layering) of nonpharmaceutical interventions; altered population susceptibility associated with prior pandemic waves; age and sex distribution; and population size and density.

**METHODS**

**Data Collection**

We combined systematic historical data collection and contemporary epidemiological and statistical analytic tools. Mortality data were obtained from the US Census Bureau’s Weekly Health Index\textsuperscript{17} for 1918-1919, a series of reports listing total deaths and death rates for 43 large US cities. These 43 cities were among the 66 most populous urban centers according to the 1920 census, and all had a population greater than 100,000. Of the 66 most populous cities, the remaining 23 had incomplete archival and mortality records. No city with a comprehensive archival record of nonpharmaceutical interventions was excluded. The Weekly Health Index is the most complete extant compilation of weekly pneumonia and influenza mortality data in US urban areas during the 1918-1919 pandemic.

In addition, we captured all of the available public health documents on nonpharmaceutical interventions implemented by these 43 cities during the 1918-1919 pandemic, including municipal public health department annual and monthly reports and weekly bulletins; every state and federal report on the 1918-1919 influenza pandemic published between 1917 and 1922; US Census pneumonia and influenza mortality data from 1910-1920; the corpus of published historical, medical, and public health literature on the 1918-1919 pandemic; 86 different newspapers from the 43 different cities; records of US military installations between 1917-1920; and additional holdings housed in several major libraries and archival repositories (the complete bibliography of the 1144 primary and secondary sources is available as an online supplement at http://www.cdc.gov/ncidod/dq/index.htm).\textsuperscript{17-23}

**Data Analysis**

From the census reports, we extracted the weekly pneumonia and influenza mortality data covering the 24 weeks from September 8, 1918, through February 22, 1919, for the 43 US cities. In 1920, these 43 cities had a combined population of approximately 23 million (22% of the total US population). A small number of missing values (846 [0.6%] of 136,563 deaths) was imputed. Using estimated weekly baseline pneumonia and influenza death rates generated from the 1910-1916 median monthly values found by Collins et al,\textsuperscript{18} weekly excess death rates (EDR) were computed. Based on available mortality data and epidemiological reports from that era, as well as a recent retrospective statistical analysis, we estimated that those who succumbed to influenza contracted it 10 days earlier.\textsuperscript{24-27}

The onset of the epidemic in a particular city was estimated as either the day of the first reported pneumonia and influenza case, or the calendar day of the first recorded pneumonia and influenza death minus 10 days, whichever was earlier. Information on nonpharmaceutical interventions was captured by reviewing at least 2 daily, high-circulation newspapers for each city and available municipal or state health reports. Nonpharmaceutical interventions were grouped into 3 major categories: school closure; public gathering bans; and isolation and quarantine. We also considered an additional general category of ancillary nonpharmaceutical interventions (eg, altering work schedules, limited closure or regulations of businesses, transportation restrictions, public risk communications, face mask ordinances).

Nonpharmaceutical interventions were considered either activated (“on”) or deactivated (“off”), according to data culled from the historical record and daily newspaper accounts. Specifically, these nonpharmaceutical interventions were legally enforced and affected large segments of the city’s population. Isolation of ill persons and quarantine of those suspected of having contact with ill persons refers only to mandatory orders as opposed to voluntary quarantines being discussed in our present era. School closure was considered activated when the city officials closed public schools (grade school through high school); in most, but not all cases, private and parochial schools followed suit. Public gathering bans typically meant the closure of saloons, public entertainment venues, sporting events, and indoor gatherings were banned or moved outdoors; outdoor gatherings were not always canceled during this period (eg, Liberty bond parades); there were no recorded bans on shopping in grocery and drug stores. Based on an estimated 10-day time frame between disease onset and death,
we estimated that the association of nonpharmaceutical interventions with reductions in EDR occurred 10 days after their actual date of implementa-
tion.3,24-27

To test the association of the layering and timing of nonpharmaceutical interven-
tions with mortality, an analysis of variance (ANOVA) model was con-
structed with weekly EDR as the depend-
ent variable and epidemiological week,
city, and the status (on/off) of every combi-
nation of nonpharmaceutical interven-
tions as the independent variables. In the
ANOVA model, each possible combina-
tion of nonpharmaceutical interventions was treated as an independent variable
to test for layering effects. Any factor with
a P value of less than .10 was included
in the model. Because there is ambigu-
ity over the rigor with which the category
of ancillary nonpharmaceutical interven-
tions was applied, enforced, and deac-
tivated, we focused primarily on the 3
major categories of nonpharmaceutical interven-
tions discussed above and we
included the ancillary nonpharmaceu-
tical interventions in the multivariate
model for purposes of completeness.

We defined additional outcome (de-
pendent) variables: (1) the time to first
peak as the time in days from the activ-
ation of the first major category of non-
pharmaceutical interventions to the date of
the first peak EDR; (2) the magni-
itude of the first peak as the first peak
weekly EDR; and (3) the mortality bur-
den as the cumulative EDR during the
entire 24-week study period.

We also defined the following inde-
dependent variables. The first was the
public health response time (PHRT) as
the time in days (either positive or nega-
tive) between the date when weekly EDR
first exceeds twice the baseline
pneumonia and influenza death rate
(2 × baseline; ie, when the mortality rate
begins to accelerate) and the activa-
tion of the first major nonpharmaceu-
tical interventions. Interventions that
occurred prior to this reference point
were recorded as negative PHRT values,
indicating that public health officials re-
sponded to events prior to the accel-
eration of weekly death rates. How-
ever, most cities had positive PHRT in
that they reacted after the 2 × baseline
mortality threshold, indicating that the
epidemic had already entered its accel-
eration phase. The second independent
variable was total days of nonpharmaceu-
tical interventions, which was defined as the total cumulative
number of days that nonpharmaceutical inter-
ventions from the 3 major cate-
gories were activated during the en-
tire 24-week study period.

The ANOVA models were based on
the study design of a 43 (city) × 24
(week) factorial design without replica-
tion. Because there is no replication, the
city × week interaction term was treated
as the error term in the multivariate analy-
sis. We considered 4 different nonphar-
maceutical interventions. Hence, there
are 15 different combinations of these
interventions (excluding the no inter-
vention combination). Each of these 15
combinations was either implemented
(on) or not implemented (off) in each
city for each week. Thus, the effects of
each of these combinations of nonphar-
maceutical interventions are included in
the city × week interaction term. Each of
these terms (along with their × city and
× week interaction terms) were extracted
from the original city × week interac-
tion term. The remaining unexplained
variation was used as the error term in
the ANOVA model. The remaining error
term is likely to be larger than a true error
term generated through replication so the
analysis of any effects using this error
term can be expected to be conserva-
tive. Such a factorial model without rep-
ication can be used to test hypotheses
but the lack of natural error in the model
makes estimates or predictions from the
model such as effect size measures and
confidence intervals nonestimable.

We also generated scatterplots and
Spearman rank correlation coefficients
to explore the associations between
PHRT and each of the 2 additional
dependent variables and associations be-
tween total days of nonpharmaceutical interven-
tions and mortality burden. We
further investigated these associations by
using box plots and Wilcoxon rank sum
tests to compare the outcomes for the cit-
ies above and below the median of each
independent variable.

We also generated scatterplots and
Spearman rank correlation coefficients
to explore other potential or confound-
ing associations (as independent deter-
ninants): (1) EDR in the 4 successive
waves of the pandemic; (2) city-specific
population size vs EDR; (3) city-
specific population density vs EDR; (4)
city-specific population age distribu-
tion vs EDR; and (5) city-specific sex dis-
bution vs EDR. Analyses were per-
formed using SAS statistical software

RESULTS
There were 115 340 excess pneumonia
and influenza deaths (EDR, 500/
100 000 population) in the 43 cities dur-
during the 24 weeks analyzed. TABLE 1
shows considerable city-to-city vari-
tion in mortality profiles and interven-
tion characteristics; lists the earliest re-
ported dates of the first pneumonia and
influenza cases by city, mortality accel-
eration (2 × baseline EDR), first imple-
mentation of nonpharmaceutical inter-
ventions, and first peak EDR; and lists
the values for each of the independent
and outcome variables described above.

TABLE 2 shows the categories of non-
pharmaceutical intervention combina-
tions, the number of cities implement-
ing those combinations, and the median
and range of duration of implementa-
tion by each of the 43 cities during the
study period. Every city adopted at least
1 of the 3 major categories of nonphar-
maceutical interventions; 15 applied all
3 categories of nonpharmaceutical inter-
ventions concurrently. School clo-
closure concurrently combined with pub-
lic gathering bans represented the most
common combination, implemented in
34 cities (79%) for a median duration of
4 weeks (range, 1-10 weeks). School
closure was ultimately used in some
combination with the other categories
of nonpharmaceutical interventions by
40 cities (93%). Three cities never of-
officially closed their schools (New York
City, New York, New Haven, Connecti-
cut, and Chicago, Illinois, although the
latter reported a student absenteism

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rate of ≥45% at the peak of its epidemic); 25 cities closed their schools once, 14 closed them twice, and 1 (Kansas City, Missouri) closed its schools 3 times. Schools were officially closed a median of 6 weeks (range, 0-15 weeks).

The ANOVA multivariate model had an $r^2$ of 86.7% ($P < .001$). Nonpharmaceutical interventions were a significant

### Table 1. Characteristics of Influenza Pandemic for 43 US Cities Between September 8, 1918, and February 22, 1919

<table>
<thead>
<tr>
<th>City</th>
<th>First Case Date</th>
<th>Mortality Acceleration Date</th>
<th>Date of First Nonpharmaceutical Intervention</th>
<th>Public Health Response Time, d</th>
<th>Total No. of Days of Nonpharmaceutical Interventions</th>
<th>Date of Peak Excess Death Rate</th>
<th>Magnitude of First Peak, Excess Deaths/100,000 Population</th>
<th>Excess Pneumonia and Influenza Mortality, Deaths/100,000 Population</th>
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</table>

*Defined as 2 × baseline death rate.
*Defined as days between 2 × baseline death rate and first nonpharmaceutical intervention.
*Weekly excess death rate.
*Total excess death rate through 24 weeks.
source of the variation in the weekly EDRs within and between the cities. The ANOVA results are shown in Table 3. The multivariate model demonstrates that layered nonpharmaceutical interventions generally had a more significant association with weekly EDR than individual nonpharmaceutical interventions. Specifically, combinations of nonpharmaceutical interventions including school closure and public gathering bans appeared to have the most significant association with weekly EDR (ie, the lowest P values, most were P < .001). The large number of significant nonpharmaceutical interventions × week interactions in the model confirms that the timing of the implementation of a given combination of nonpharmaceutical interventions was a significant factor in reducing morality. One caveat is persistent nonpharmaceutical interventions × city interactions, meaning that the success of a strategy of nonpharmaceutical interventions in a particular city does not uniformly translate to all other cities. The 2 outlier cities in our study, Grand Rapids, Michigan, and St Paul, Minnesota, exemplify this point.

The scatterplots in Figure 1A, Figure 1B, and Figure 1C display the associations between the PHRT and each of the 3 dependent variables. Figure 1A displays the association between PHRT in days and time to first peak EDR; cities that implemented nonpharmaceutical interventions earlier had greater delays in reaching peak mortality (Spearman r = −0.74, P < .001). Figure 1B shows the association between PHRT and the magnitude of the first peak EDR; cities that implemented nonpharmaceutical interventions earlier had lower peak mortality rates (Spearman r = 0.31, P = .02). Figure 1C depicts the association between PHRT and total mortality burden; cities that implemented nonpharmaceutical interventions earlier experienced a lower total mortality (Spearman r = 0.37, P = .008). In summary, when comparing the 21 cities with earlier (less than the median) PHRT with the 21 cities with the later (greater than the median) PHRT, there are statistically significant differences for each of the outcome measures (P ≤ .001; Table 4).

Figures 1C and 1D show the association between early, sustained, and layered application of nonpharmaceutical interventions and total excess pneumonia and influenza mortality burden in 43 cities. Figure 1C shows the statistically significant association between PHRT and total mortality burden. Figure 1D shows a statistically significant association between increased duration of nonpharmaceutical interventions and a reduced total mortality burden (Spearman r = −0.39, P = .005). In summary, the 21 cities that had earlier PHRT (ie, less than the median) and the most sustained and most days of nonpharmaceutical interventions had a statistically significant reduction in excess pneumonia and influenza mortality rates compared with the 21 cities that had later PHRT and fewer days of nonpharmaceutical interventions (Table 4).

Figure 2 shows the aggregate city mortality curves by region (East, Midwest, and West, and South). Figure 3 displays 4 city-specific mortality curves, including weekly EDR and the nonpharmaceutical interventions implemented as well as their activation and deactivation dates for St Louis, Missouri, New York City, Denver, Colorado, and Pittsburgh, Pennsylvania. These 4 cities were chosen because they indicate the broad spectrum of outcomes seen in the 43 cities studied as well as for their geographical and social diversity. (The mortality curves for all 43 cities are available at http://www.cdc.gov/ncidod/dq/index.htm.) Overall, cities that implemented nonpharmaceutical interventions earlier experienced associated delays in the time to peak mortality, reductions in the magnitude of the peak mortality, and decreases in the total mortality burden.

In exploring alternative and potentially confounding explanations for variation in city-specific EDR, we used a scatterplot to compare the cumulative EDR of the 43 cities during pandemic waves 1 (February–May 1918), 2 (September–December 1918), 3 (January–April 1919), and 4 (January–April 1920). We found no statistically significant association of the EDR across the 43 cities when comparing successive waves. Specifically, the severity or occurrence of wave 1 is not associated, either positively or negatively, with the severity of wave 2; the severity of wave 2 is not associated with the severity of wave 3; and the severity of wave 3 is not associated with the severity of wave 4 (figures appear in the online supplement at http://www.cdc.gov/ncidod/dq/index.htm).28,29

Published virologic evidence for strain variation during wave 2 is limited to a single genotypic variant without evidence for significant phenotypic change in virulence. While plausible, no virologi-
cal evidence yet exists to explain the perplexing mortality difference between the spring 1918 wave, which was reportedly milder, and the subsequent fall and winter waves. Additional studies may clarify the understanding of the 1918 pandemic’s wave phenomena.

Similarly, scatterplots comparing the cumulative EDR to the city-specific population size and density; sex distribution; and proportion of ages of younger than 1 month to 5 years, 15 to 40 years, and older than 65 years, which corresponded to high reported specific mortality rates in 1918 demonstrated no association. Among the 43 cities we investigated, neither the city’s population size, density, sex distribution, nor age distribution accounted for the differences in mortality (figures appear in supplement at http://www.cdc.gov/ncidod/dq/index.htm).

Table 3. Multivariate Model Showing Effect of Combinations of Nonpharmaceutical Interventions on Weekly Excess Death Rates for 43 US Cities Between September 8, 1918, and February 22, 1919

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>df</th>
<th>Sum of Squares</th>
<th>Mean Square</th>
<th>F Score</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of confounders Week</td>
<td>29</td>
<td>75,677.0</td>
<td>2609.6</td>
<td>16.24</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>City</td>
<td>42</td>
<td>65,567.9</td>
<td>1560.9</td>
<td>9.72</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1 Nonpharmaceutical intervention School closure</td>
<td>1</td>
<td>1288.7</td>
<td>1288.7</td>
<td>8.02</td>
<td>.005</td>
</tr>
<tr>
<td>× Week</td>
<td>8</td>
<td>4551.8</td>
<td>569.0</td>
<td>3.54</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Banning public gatherings</td>
<td>1</td>
<td>1342.0</td>
<td>1342.0</td>
<td>8.35</td>
<td>.004</td>
</tr>
<tr>
<td>Isolation and quarantine</td>
<td>1</td>
<td>911.1</td>
<td>911.1</td>
<td>5.67</td>
<td>.02</td>
</tr>
<tr>
<td>× City</td>
<td>10</td>
<td>3976.5</td>
<td>397.7</td>
<td>2.48</td>
<td>.006</td>
</tr>
<tr>
<td>Ancillary nonpharmaceutical interventions</td>
<td>1</td>
<td>897.3</td>
<td>897.3</td>
<td>5.59</td>
<td>.02</td>
</tr>
<tr>
<td>× Week</td>
<td>13</td>
<td>6122.4</td>
<td>471.0</td>
<td>2.93</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>× City</td>
<td>12</td>
<td>10,257.6</td>
<td>854.8</td>
<td>5.32</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2 Nonpharmaceutical interventions School closure and banning public gatherings</td>
<td>1</td>
<td>681.3</td>
<td>681.3</td>
<td>4.24</td>
<td>.04</td>
</tr>
<tr>
<td>× Week</td>
<td>9</td>
<td>6497.0</td>
<td>721.9</td>
<td>4.49</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>× City</td>
<td>13</td>
<td>6229.9</td>
<td>479.2</td>
<td>2.98</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>School closure and isolation and quarantine</td>
<td>1</td>
<td>2335.3</td>
<td>2335.3</td>
<td>14.54</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>× Week</td>
<td>4</td>
<td>2434.2</td>
<td>608.6</td>
<td>3.79</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Banning public gatherings and isolation and quarantine</td>
<td>1</td>
<td>292.3</td>
<td>292.3</td>
<td>1.82</td>
<td>.18</td>
</tr>
<tr>
<td>× Week</td>
<td>1</td>
<td>563.9</td>
<td>563.9</td>
<td>3.51</td>
<td>.06</td>
</tr>
<tr>
<td>Banning public gatherings and ancillary nonpharmaceutical interventions</td>
<td>1</td>
<td>272.6</td>
<td>272.6</td>
<td>1.70</td>
<td>.19</td>
</tr>
<tr>
<td>× Week</td>
<td>4</td>
<td>7444.6</td>
<td>1861.1</td>
<td>11.59</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>× City</td>
<td>4</td>
<td>5547.6</td>
<td>1386.9</td>
<td>8.63</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Isolation and quarantine and ancillary nonpharmaceutical interventions</td>
<td>1</td>
<td>48.1</td>
<td>48.1</td>
<td>0.30</td>
<td>.58</td>
</tr>
<tr>
<td>× Week</td>
<td>2</td>
<td>1507.6</td>
<td>753.8</td>
<td>4.69</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>× City</td>
<td>2</td>
<td>824.7</td>
<td>412.4</td>
<td>2.57</td>
<td>.08</td>
</tr>
<tr>
<td>3 Nonpharmaceutical interventions School closure, banning public gatherings, and isolation and quarantine</td>
<td>1</td>
<td>762.4</td>
<td>762.4</td>
<td>4.75</td>
<td>.03</td>
</tr>
<tr>
<td>× Week</td>
<td>2</td>
<td>2239.3</td>
<td>1119.7</td>
<td>6.97</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>School closure, banning public gatherings, and ancillary nonpharmaceutical interventions</td>
<td>1</td>
<td>691.6</td>
<td>691.6</td>
<td>4.41</td>
<td>.04</td>
</tr>
<tr>
<td>× Week</td>
<td>10</td>
<td>12,260.5</td>
<td>1226.0</td>
<td>7.63</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>× City</td>
<td>26</td>
<td>51,423.8</td>
<td>1977.8</td>
<td>12.31</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>School closure, isolation and quarantine, and ancillary nonpharmaceutical interventions</td>
<td>1</td>
<td>3451.1</td>
<td>3451.1</td>
<td>21.48</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>× Week</td>
<td>4</td>
<td>2493.5</td>
<td>623.4</td>
<td>3.88</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Banning public gatherings, isolation and quarantine, and ancillary nonpharmaceutical interventions</td>
<td>1</td>
<td>51.9</td>
<td>51.9</td>
<td>0.32</td>
<td>.57</td>
</tr>
<tr>
<td>× Week</td>
<td>8</td>
<td>4535.2</td>
<td>566.9</td>
<td>3.53</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>4 Nonpharmaceutical interventions School closure, banning public gatherings, isolation and quarantine, and ancillary nonpharmaceutical interventions</td>
<td>1</td>
<td>503.7</td>
<td>503.7</td>
<td>3.14</td>
<td>.08</td>
</tr>
<tr>
<td>× Week</td>
<td>9</td>
<td>6068.3</td>
<td>674.3</td>
<td>4.20</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>× City</td>
<td>13</td>
<td>23,097.7</td>
<td>1080.4</td>
<td>11.26</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Error</td>
<td>770</td>
<td>123,691.2</td>
<td>160.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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COMMENT

During the 1918-1919 influenza pandemic, all 43 cities eventually implemented nonpharmaceutical interventions but the time of activation, duration, and choice or combination of these nonpharmaceutical interventions appear to have been key factors in their success or failure. In 1918, decisions to activate nonpharmaceutical interventions were typically triggered by excess morbidity, mortality, or both, as well as situational awareness of other communities near and far. Because discerning precisely the first arrival of pandemic virus in a community was difficult, we chose to measure public health response time in reference to excess pneumonia and influenza mortality (ie, when weekly EDR first crossed the threshold of 2 × the baseline and the mortality rates entered an acceleration phase).

Table 4. Implementation Strategy of Nonpharmaceutical Interventions for 21 Cities Between September 8, 1918, and February 22, 1919

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Early (&lt;7 d)</th>
<th>Late (≥7 d)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to peak, d</td>
<td>13</td>
<td>9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Magnitude of first peak (weekly EDR)</td>
<td>54.7</td>
<td>101.5</td>
<td>.001</td>
</tr>
<tr>
<td>Excess pneumonia and influenza mortality rate (total EDR)</td>
<td>359.1</td>
<td>529.5</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: EDR, excess death rate.
Hence, the difference in time between the first nonpharmaceutical interventions and this excess mortality threshold may be a positive or negative value. For example, in Philadelphia, Pennsylvania, which was affected early and was unprepared to respond, the PHRT was 8 and the EDR was approximately 37/100,000 population at the point of implementing nonpharmaceutical interventions; in contrast, New York City’s PHRT was −11 days and the EDR was 0/100,000 population at the point of implementing nonpharmaceutical interventions. New York City responded to its first influenza cases and the perceived severity of the epidemic in nearby cities without waiting for excess deaths to accumulate.

The US Centers for Disease Control and Prevention’s newly released interim community mitigation guidance recommends activating nonpharmaceutical interventions when outbreaks due to a pandemic virus strain first are confirmed in a state or metropolitan service region.36 Several theoretical models suggest that the effect of targeted, layered strategies for nonpharmaceutical interventions may be optimized when community influenza attack rates are 1% or lower.11,12 Given the exponential growth of an unmitigated influenza pandemic, it is reasonable to expect that the timing of interventions will be among the most critical factors. Such expectations and biological realities are consistent with our observations of the 1918 pandemic, when rapid public health response time was a critical factor in the successful application of nonpharmaceutical interventions.

Late interventions, regardless of their duration or permutation of use, almost always were associated with worse outcomes. However, timing alone was not consistently associated with success. The combination and choice of nonpharmaceutical interventions also appeared to be critical as confirmed by the multivariate model.

For example, New York City reacted earliest to the gathering influenza crisis, primarily with the sustained (>10 weeks beginning September 19, 1918) and rigidly enforced application of compulsory isolation and quarantine procedures, along with an enforced staggered business hour ordinance from October 5 through November 3, 1918.39 During this era, New York City’s health department was renowned internationally for its innovative policies of mandatory case reporting and rigidly enforced isolation and quarantine procedures.35 Typically, individuals diagnosed with influenza were isolated in hospitals or makeshift facilities, while those suspected to have contact with an ill person (but who were not yet ill themselves) were quarantined in their homes with an official placard declaring that location to be under quarantine. New York City mounted an early and sustained response to the epidemic and experienced the lowest death rate on the Eastern seaboard but it did not layer its response. New York City’s cumulative mortality burden, 452/100,000, ranked 15 out of the 43 cities during the study period.

However, the benefits of these interventions were not equally distributed. Those cities acting in a timely and comprehensive manner appear to have benefited most in terms of reductions in total EDR. For example, St Louis, which implemented a relatively early, layered strategy (school closure and cancellation of public gatherings), and sustained these nonpharmaceutical interventions for about 10 weeks each, did not experience nearly as deleterious an outbreak as 36 other communities in the study (cumulative EDR = 358/100,000 population).

The 1918 experience suggests that sustained nonpharmaceutical interventions are beneficial and need to be “on” throughout the particular peak of a local experience. Many of the 43 cities in the study, particularly in the Midwest and South and West, experienced 2 peaks of excess pneumonia and influenza mortality (eg, Birmingham, Alabama, Cincinnati, Ohio, Columbus, Ohio, Denver, Indianapolis, Indiana, Kansas City,
Louisville, Kentucky, Milwaukee, Wisconsin, Minneapolis, Minnesota, Oak-
land, California, Omaha, Nebraska, Portland, Oregon, Rochester, New York, St
Louis, San Francisco, California, Se-
ette, Washington, Spokane, Washing-
ton, Toledo, Ohio; see figures in online
supplement at http://www.cdc.gov/ncidod/dq/index.htm). These second

Figure 3. Weekly Excess Death Rates From September 8, 1918, Through February 22, 1919

Type and duration of nonpharmaceutical interventions are indicated under each plot. For the specific nonpharmaceutical interventions, black bars indicate activation.

- School closure
- Public gathering ban
- Other

- School closure
- Public gathering ban
- Isolation, quarantine
- Other

- Business hours restricted, streetcars' capacity limited.
- Staggered business hours, signs with “cover coughs.”
- Staggered business hours, warning signs posted in theaters.
- School children given information to take home, warned not to gather in groups.
peaks frequently followed the sequential activation, deactivation, and reactivation of nonpharmaceutical interventions, highlighting the transient protective nature of nonpharmaceutical interventions and the need for a sustained response. For example, Denver (cumulative EDR=631/100 000 population) responded twice with an extensive menu of nonpharmaceutical interventions that included public gathering bans, school closure, isolation and quarantine, and several ancillary nonpharmaceutical interventions and these actions are reflected temporally in its 2-peak mortality curve.

Such dual-peaked cities are of particular interest because of the specificity and temporal associations between excess mortality and the triggers of activation and deactivation of nonpharmaceutical interventions and the implications for a causal relationship. Among the 43 cities, we found no example of a city that had a second peak of influenza while the first set of nonpharmaceutical interventions were still in effect, suggesting that each city with a bimodal pattern served as its own control. In dual-peaked cities, activation of nonpharmaceutical interventions was followed by a diminution of deaths and, typically, when nonpharmaceutical interventions were deactivated, death rates increased.

History is not a predictive science. There exist numerous well-documented and vast differences between US society and public health during the 1918 pandemic compared with the present. We acknowledge the inherent difficulties of interpreting data recorded nearly 90 years ago and contending with the gaps, omissions, and errors that may be included in the extant historical record. The associations observed are not perfect; for example, 2 outlier cities (Grand Rapids and St Paul) experienced better outcomes with less than perfect public health responses. Future work by our research team will explore social, political, and ecological determinants, which may further help to explain some of this variation.

The United States of 1918 had many similar features to the present era: rapid transportation in the form of trains and automobiles; rapid means of communication in the form of the telegraph and telephone; large, heterogeneous populations with substantial urban concentrations (although a much higher percentage of the US population lived in rural areas compared with the present); a news system that was able to circulate information widely during the epidemic, including many daily newspapers and broadsheets distributed in communities; and a wide spectrum of public health agencies at various levels of government.

When examining the 1918 pandemic, however, it is important to recognize the numerous social, cultural, and scientific differences that do exist between that period and the present. For example, the legal understanding of privacy, civil, and constitutional rights as they relate to public health and governmentally directed measures (such as mass vaccination programs) has changed markedly over the past 90 years. In addition, public support of and trust in these measures, along with trust in the medical profession as a whole, has shifted over time. Finally, other features of the modern era that need to be considered when applying lessons from history to the present era include the increased speed and mode of travel, above all high-volume commercial aviation; instantaneous access to information via the Internet and personal computers; a baseline understanding among the general population that the etiologic agents of infectious diseases are microbial; and advances in medical technology and therapeutics that have expanded considerably the options available for dealing with a pandemic.

Historical contextual issues and statistical limitations aside, the US urban experience with nonpharmaceutical interventions during the 1918-1919 pandemic constitutes one of the largest data sets of its kind ever assembled in the modern, postgerm theory era.

Our findings conform to 8 of A. Bradford Hill’s 9 tenets on causal associations in the consideration of disease and the environment. Specifically, during the 1918-1919 pandemic, the relation of early, sustained, and layered nonpharmaceutical interventions to EDR in 43 US cities demonstrate satisfaction of the criteria of strength (the magnitude and statistical significance of our findings, which also argue against an association by chance alone), consistency (early and combined nonpharmaceutical interventions were consistently associated with reductions in mortality, and our analysis is consistent with 2 recent smaller, preliminary historical epidemiological reports, although these studies look at only 16 US urban centers, do not include actual activation and deactivation time points, duration, or layering of nonpharmaceutical interventions, and rely extensively on secondary historical sources.37,38

Further, our retrospective study is consistent with the results from recent theoretical models of the spread of a contemporary pandemic, which highlight the value of early, combined, and sustained nonpharmaceutical interventions to mitigate a pandemic11-15), specificity (best demonstrated in cities with bimodal mortality peaks when the triggers were activated, deactivated, and reactivated), temporality (interventions always preceded the reduction of EDR), dose response (layering and increased duration of the nonpharmaceutical interventions were associated with better outcomes), biological plausibility (these interventions reduce person-to-person interactions and biologically would be expected to reduce the spread of a communicable agent such as influenza), coherence (our data align with the established body of knowledge on the epidemiology of influenza), and analogy (isolation and social distancing have been demonstrated as effective means of preventing person-to-person spread of other respiratory tract diseases, such as rhinovirus, severe acute respiratory syndrome, respiratory syncytial virus, varicella, and seasonal influenza).

The ninth tenet, experiment, could not be demonstrated directly because of the paucity of influenza pandemics in the past century, the trend away from such traditional public health meas-
sures for disease control during the past 50 years, and ethical limitations of using population-wide nonpharmaceutical interventions in the absence of a serious threat.

These findings contrast with the conventional wisdom that the 1918 pandemic rapidly spread through each community killing everyone in its path. Although these urban communities had neither effective vaccines nor antivirals, cities that were able to organize and execute a suite of classic public health interventions before the pandemic swept fully through the city appeared to have an associated mitigated epidemic experience. Our study suggests that nonpharmaceutical interventions can play a critical role in mitigating the consequences of future severe influenza pandemics (category 4 and 5) and should be considered for inclusion in contemporary planning efforts as companion measures to developing effective vaccines and medications for prophylaxis and treatment. The history of US epidemics also cautions that the public’s acceptance of these health measures is enhanced when guided by ethical and humane principles.30–41

Author Contributions: Drs Markel and Cetron had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Markel, Lipman, Navarro, Stern, Cetron.

Acquisition of data: Markel, Navarro, Sloan, Michalsen, Stern.

Analysis and interpretation of data: Markel, Lipman, Navarro, Sloan, Michalsen, Cetron.

Drafting of the manuscript: Markel, Lipman, Navarro, Sloan, Michalsen, Stern, Cetron.

Critical revision of the manuscript for important intellectual content: Markel, Lipman, Navarro, Stern, Cetron.

Statistical analysis: Markel, Lipman, Cetron.

Obtained funding: Markel, Cetron.

Administrative, technical, or material support: Markel, Navarro, Sloan, Michalsen, Cetron.

Study supervision: Markel, Cetron.

Financial Disclosures: None reported.

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Role of the Sponsor: The US Centers for Disease Control and Prevention provided funding as part of pandemic preparedness research. Drs Cetron and Lipman from the Division of Global Migration and Quarantine at the Centers for Disease Control and Prevention participated as full scientific collaborators in the investigation.

Acknowledgment: Matthew Cartter, MD, MPH, Cleto DiGiovanni Jr, Jeffrey Duchin, MD, Bruce Gel-
Saturated fatty acids increase levels of low-density lipoprotein cholesterol (LDL-C) and HDL-C, whereas trans-fatty acids increase LDL-C level but decrease HDL-C level. This distinction is important, because trans-fatty acids are more strongly associated with the risk of cardiovascular disease than saturated fatty acids due to their undesirable effects on LDL-C and HDL-C levels, endothelial cell function, adipocytes, and inflammatory response.

In Reply: Dr Kim distinguishes the effects of saturated fatty acids and trans-fatty acids on lipoproteins. However, reports of the effect of trans-fatty acids on HDL-C have been variable, with a large meta-analysis finding a statistically non-significant effect on HDL-C. In addition to increasing levels of LDL-C, trans-fatty acids promote vascular inflammation and endothelial dysfunction and reduce paraoxonase activity. These lipid and biochemical effects act synergistically to increase cardiovascular disease risk.

The issue is more complex than indicated by HDL-C. Saturated fat rapidly promotes proinflammatory changes in HDL without changing HDL-C level. Thus, as mentioned in our review, dietary intake of both saturated fatty acids and trans-fatty acids should be avoided and substituted with intake of monounsaturated and polyunsaturated fatty acids.

Benjamin J. Ansell, MD
Department of Medicine
David Geffen School of Medicine at UCLA
Los Angeles, California

Financial Disclosures: Dr Ansell reported receiving speaking honoraria from AstaZeneca, Kos Pharmaceuticals, Merck, and Pfizer; receiving research medication from Merck and Pfizer in the past; and having equity interest in Bruin Pharma. No other disclosures were reported.


CORRECTIONS

Data Error: In the Review article entitled “Data Extraction Errors in Meta-analyses That Use Standardized Mean Differences” published in the July 25, 2007, issue of JAMA (2007;298:430-437), Figure 4 included incorrect data. The reported point estimate and its 95% confidence interval for the meta-analysis standardized mean differences “−0.74 (−0.98 to −0.49)” for the Edmonds et al article should have read “−0.77 (−1.26 to −0.28).” The error was caused by a wrong label in the Cochran eLibrary at the time of the study. A meta-analysis was stated to have been done with a random-effects model; however, it was done with a fixed-effect model. The Cochran eLibrary no longer contains this error.

Typographical Errors in Tables: In the Research Letter entitled “Patterns of Prevalent Major Chronic Disease Among Older Adults in the United States” published in the September 12, 2007, issue of JAMA (2007;298:1160-1162), both tables contained typographical errors. In both tables, the column headings of “Estimated Frequency (× 1000)” and “CVA” were erroneously transposed and the brace under the column head “Disease Pattern, No. of Diseases” should have extended to include the CVA column. Online versions of this article on the JAMA Web site were corrected on October 4, 2007.

Incorrect Affiliation: In the Research Letter entitled “Cardiovascular Response to a Modern Roller Coaster Ride” published in the August 15, 2007, issue of JAMA (2007;298:739-741), the affiliations were reversed for 2 authors and 1 author’s name was listed out of order. Joachim Brade, MSc, is affiliated with the Department of Medical Statistics and Dariusch Haghi, MD, is affiliated with the 1st Department of Medicine-Cardiology, University Hospital of Mannheim, Mannheim, Germany. The name for Christian Wolpert, MD, should have been placed last among the list of author names.

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