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Surges of advanced medical support associated with influenza outbreaks

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SUMMARY

We utilized de-identified data to evaluate increases in four outcomes during influenza outbreak periods (IOPs) including: hospitalization, intensive care unit admission, mechanical ventilation or death for adults aged 18 years or older with medically attended acute respiratory illnesses (MAARI) admitted to any of Maryland's 50 acute-care hospitals over 12 years. Weekly numbers of positive influenza tests in the Maryland area were obtained from the US Center for Disease Control and Prevention interactive website. The fewest consecutive weeks around the peak week containing at least 85% of the positive tests defined the IOP. Weekly counts of individual study outcomes were positively correlated with regional weekly counts of positive influenza tests during all the IOPs over 12 years. Also, rate ratios comparing daily occurrences of each study outcome between the IOP and non-IOP were significantly elevated. These results confirm conclusions of previous studies that influenza outbreaks are clearly associated with deaths and increased use of advanced medical resources by patients with MAARI. These data analyses suggest that increased efforts to develop more effective influenza vaccines and therapeutics should be a priority.

Key words: Death, hospitalization, influenza, intensive care unit, mechanical ventilation, medical support.

INTRODUCTION

Influenza illnesses are estimated to occur in 5–20% of the population and are a substantial cause of worldwide morbidity and mortality every year [1–4]. In addition, influenza outbreaks impose a considerable economic burden. In the USA influenza-related illnesses are estimated to result in costs of US$ 87 billion annually, with over US$ 6 billion related to direct hospital care [1, 5].

Multiple publications have reported the association of seasonal and pandemic influenza outbreaks with increased utilization of advanced medical care including hospitalization, intensive care unit (ICU) admissions, mechanical ventilation or deaths as individual factors [2, 6–11]. However, simultaneous evaluation of surges of all four outcomes in a large fixed population showing their relationship to yearly influenza outbreaks over multiple years has not been reported.

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The objective of this investigation was to simultaneously evaluate temporal increases of each of these four advanced medical support outcomes during influenza outbreaks and to show their relationship to regional influenza virus surveillance data reported by the US Centers for Disease Control and Prevention (CDC) over multiple years. Information about temporal increases of these study outcomes was obtained from inpatient medical support and outcome data collected from all 50 Maryland acute-care hospitals over 12 consecutive study years. This allowed a longitudinal evaluation of the relationship between demand for medical resources and the timing of influenza seasons dominated by different influenza strains or types and of varying intensity, including the A/H1N1 pandemic (H1N1pdm) during the 2008–2009 and 2009–2010 seasons.

SUBJECTS AND METHODS

Study data

The study database included all adult patients admitted to any of the 50 Maryland state-regulated acute-care hospitals over 12 consecutive study years from 1 July 2001 through 29 June 2013. Importantly, these hospitals represent a spectrum of community, teaching and public acute-care medical centers [12]. Bed capacity for these acute-care hospitals ranged from 9 to 1000 and adult critical care beds from 0 to 266. The State of Maryland's Health Services Cost Review Commission (HSCRC) provided data on advanced medical support and death as well as diagnostic codes for all hospitalized patients for all 12 study years [13]. The HSCRC was established by Maryland law in 1971 and was given broad responsibility regarding public disclosure of hospital data to promote, among other factors, cost containment, access to care, and equity. Maryland Veterans Hospitals were not included in the investigation because they are not under state regulation and therefore HSCRC data were not available.

All data extracted from the HSCRC database were de-identified. Extracted data included demographic information such as patient admission date, age in years, gender and race. This database contained information on the study's four key outcomes including hospitalization, ICU admission, intubated mechanical ventilation and death during each patient's hospital stay. Current Procedural Terminology (CPT) codes 96·70, 96·71, and 96·72 were used to identify patients who received continuous mechanical ventilation.

Study population

The study population included all patients aged 18 years and older hospitalized in any of the 50 Maryland state-regulated acute-care hospitals with the possible diagnosis of influenza. Since patients with influenza infections most often present with signs and symptoms of respiratory-related illnesses, data for the population with medically attended acute respiratory illness (MAARI) or influenza as at least part of their hospital diagnoses were analyzed. Identification of patients with MAARI-related diagnoses was accomplished by using International Classification of Diseases version nine (ICD-9) codes of interest in a manner previously described [10, 14]. MAARI-related diagnoses included one or more primary or subsequent ICD-9 discharge codes for upper, middle and lower respiratory illnesses, as well as specific codes for fever, respiratory viral illness and influenza. Data on influenza testing on individual patients were not available in the database used.

Study intervals of interest

US Morbidity and Mortality Weekly Report (MMWR) designated weeks were utilized to define influenza seasons for 12 consecutive years from 2001–2002 through 2012–2013 [15, 16]. A study year started at the beginning day of MMWR week 27 (late June or early July) of 1 year and ended on the last day of MMWR week 26 (late June or early July) of the following year in order to capture at least one full influenza season. Influenza virus surveillance data for the 12 study years were obtained from the CDC interactive website for Health and Human Services (HHS) Region 3 that included Maryland, as well as Delaware, District of Columbia, Pennsylvania, Virginia, and West Virginia [17].

Weekly influenza positive test counts were used to define two discrete time periods for the analyses for each study year. The influenza outbreak period (IOP) consisted of the fewest number of consecutive MMWR weeks, including the peak week with at least 85% of the positive influenza tests for US Department of HHS Region 3 for each of the 12 individual seasons. The non-influenza outbreak period (NIOP) included the remaining weeks on either 'side' of the IOP for each study-defined year.

For this investigation, study year 2008–2009 began on 1 July 2008 and ended on 4 July 2009. This study year was anomalous in that it captured two distinct

IOPs. The first IOP was the seasonal influenza outbreak from 15 February 2009 to 14 March 2009. The second IOP was the initial 'wave' of the A/H1N1pdm virus, which occurred from 7 June 2009 to 4 July 2009. Study year 2009–2010 started 5 July 2009 and ended 4 July 2010 and included the major A/H1N1pdm virus second wave with an IOP from 11 October 2009 to 7 November 2009.

Data analyses

The first descriptive analysis involved visual examination of whether surges of each of the four individual study outcomes in patients hospitalized with MAARI-related diagnoses were temporally related to increases in positive influenza tests in the Maryland vicinity (HHS Region 3). This examination was based upon weekly counts of each of the four key study outcomes in relation to simultaneous weekly counts of positive influenza tests during the IOPs for the 12 study years combined.

In addition, the strength of the relationship between MAARI-related outcomes and the intensity of the influenza epidemic was assessed. Spearman's rank correlation coefficients (CCs) were calculated between the numbers of weekly positive influenza tests and concomitant weekly counts of each of the four individual study outcomes during the IOPs over the 12 study years. CCs were also calculated for influenza A subtypes or for B strains. B strains were not differentiated between B Yamagata or B Victoria lineage. These analyses included all adults 18 years of age and older analyzed together as well as divided into three age subgroups: 18 to <50 years; 50 to <65 years; and 65 years and older.

In addition, rate ratios (RR) based on the number of daily counts of each MAARI-related outcomes were estimated between all the IOP and NIOP intervals for the 12 study years combined. A Poisson regression model was used to estimate the RR and associated *P* values of each of the four study outcomes for the IOPs compared with NIOPs for the 12 study years combined. In addition to the IOP indicator, the regression model included admission year and month to account for seasonal variability that likely involved a mixture of factors. These factors may have included influenza, other respiratory pathogens, as well as seasonal or environmental issues that could have influenced the outcome measures of interest. The RR was considered a quantitative indicator of surge of these study outcomes during the IOP *vs.* the NIOP. The estimation of RR was conducted for all adults and also for each of the three adult age subgroups as previously described.

All the data analyses were performed using the SAS software (version 9.3, SAS Institute).

Human subject protection

All data regarding influenza surveillance and hospitalization were examined and analyzed without personal identifiers. This study was reviewed and approved by the Institutional Review Board of the University of Maryland at Baltimore.

RESULTS

Table 1 demonstrates the demographics of 7 474 837 adult patients admitted to any of Maryland's acute-care hospitals over the 12 study years. More females than males were hospitalized overall. In the 18 to <50 years of age group, twice as many females as males were hospitalized. This female predominance was likely due to women admitted for labor and delivery. White race accounted for 61·9% of the subjects.

Using data from both Tables 1 and 2, 967 767 (12·9%) of total hospitalizations were MAARI related. Out of 967 767 MAARI-related hospitalizations, 124 240 (12·85%) patients were admitted to an ICU; 97 446 (10·1%) received mechanical ventilation, and 56 327 (5·8%) died in the hospital. The percentage of total hospital admissions with MAARI-related illnesses increased with advancing age with 8·2%, 13·6%, and 17·4% of adults aged 18 to <50, 50 to <65, and >65 years, respectively.

Figure 1 displays four subplots, one for each of the four study outcomes in relation to weekly counts of HHS Region 3 positive influenza tests for 12 consecutive influenza study years. These subplots illustrate that seasonal peaks of positive influenza tests were closely associated with simultaneous peaks of the four individual study outcomes of interest.

Table 3 shows Spearman's CCs between weekly counts of each of the four MAARI-related study outcomes and the weekly counts of all positive influenza tests in HHS Region 3 within the IOPs over the 12 study years combined for all adults and for the three age subgroups. In addition, CCs are presented for the three individual circulating influenza outbreak virus types or subtypes for the 12 study years. Positive correlations were identified for all four study outcomes for all ages combined. In addition, all CCs

Table 1. *Demographics of hospitalized patients*

	All adults	18 to <50 years	50 to <65 years	65 years and above
Total hospitalizations, *n*	7 474 837	2 901 730	1 726 188	2 846 919
Gender, *n* (%)				
Male	3 018 159 (40·4)	962 476 (33·2)	860 905 (49·9)	1 194 778 (42·0)
Female	4 456 528 (59·6)	1 939 151 (66·8)	865 256 (50·1)	1 652 121 (58·0)
Unknown	150 (0·0)	103 (0·0)	27 (0·0)	20 (0·0)
Race, *n* (%)				
White	4 625 957 (61·9)	1 496 038 (51·6)	1 045 257 (60·6)	2 084 662 (73·2)
African-American	2 386 330 (31·9)	1 125 076 (38·8)	605 995 (35·1)	655 259 (23·0)
Asian or Pacific Islander	122 157 (1·6)	68 285 (2·4)	19 090 (1·1)	34 782 (1·2)
American-Indian	17 040 (0·2)	8851 (0·3)	3779 (0·2)	4410 (0·2)
Other	305 902 (4·1)	195 289 (6·7)	48 206 (2·8)	62 407 (2·2)

Table 2. *Rate ratios (RR)*[a] *of admissions with MAARI-related study outcomes for all 12 study years*

	All adults	18 to <50 years	50 to <65 years	65 years and above
Hospitalization				
Number	967 767	237 176	234 168	496 423
RR (95% CI)	1·119 (1·103–1·135)	1·145 (1·125–1·165)	1·121 (1·100–1·142)	1. 106 (1·089–1·123)
P value	<0·0001	<0·0001	<0·0001	<0·0001
ICU admission				
Number	124 240	24 328	34 642	65 270
RR (95% CI)	1·085 (1·063–1·108)	1·121 (1·080–1·165)	1·089 (1·052–1·126)	1·070 (1·043–1·098)
P value	<0·0001	<0·0001	<0·0001	<0·0001
Mechanical ventilation				
Number	97 446	20 397	27 278	49 771
RR (95% CI)	1·109 (1·087–1·163)	1·117 (1·073, 1·163)	1·123 (1·085–1·162)	1·097 (1·068–1·127)
P value	<0·0001	<0·0001	<0·0001	<0·0001
Death				
Number	56 327	4989	10 705	40 633
RR (95% CI)	1·125 (1·097–1·153)	1·163 (1·075–1·258)	1·131 (1·071–1·195)	1·118 (1·086–1·151)
P value	<0·0001	0·0002	<0·0001	<0·0001

[a] RR, 95% CI, and *P* value were estimated by comparing daily counts of each of the four study outcomes associated with medically attended acute respiratory illness (MAARI) between the influenza outbreak period to non-influenza outbreak periods.

for the age subgroups were positive with values that ranged from 0·282 to 0·594 with the exception of death for patients 18 to <50 years of age where the CC was only mildly elevated 0·066. CC's between death and weekly influenza-positive tests generally trended to be more positive with increasing age.

Table 3 further demonstrates that influenza virus subtypes and types were associated with a mixture of study outcome patterns. For A/H1N1 viruses, generally higher positive CCs between positive influenza tests and counts of the all outcomes except death were observed for the two younger age groups compared with the oldest group, aged 65 years and older. Correlation coefficients were generally more positive for A/H3N2 and B viruses than for A/H1N1 virus for patients 65 years of age or older. Also, influenza B viruses were associated with relatively similar increases in CCs for the study outcomes as the influenza A/H3N2 virus in these hospitalized patients.

Table 2 displays the estimated RRs for MAARI-related study outcomes during the IOPs compared with NIOPs for all 12 study years combined. For adults of all ages combined, the RRs were significantly elevated for all four study outcomes during the IOPs compared with NIOPs, with RRs ranging from 1·085 to 1·125 and all *P* values <0·0001. Also, each age subgroup had significantly elevated RRs for all four outcomes including the

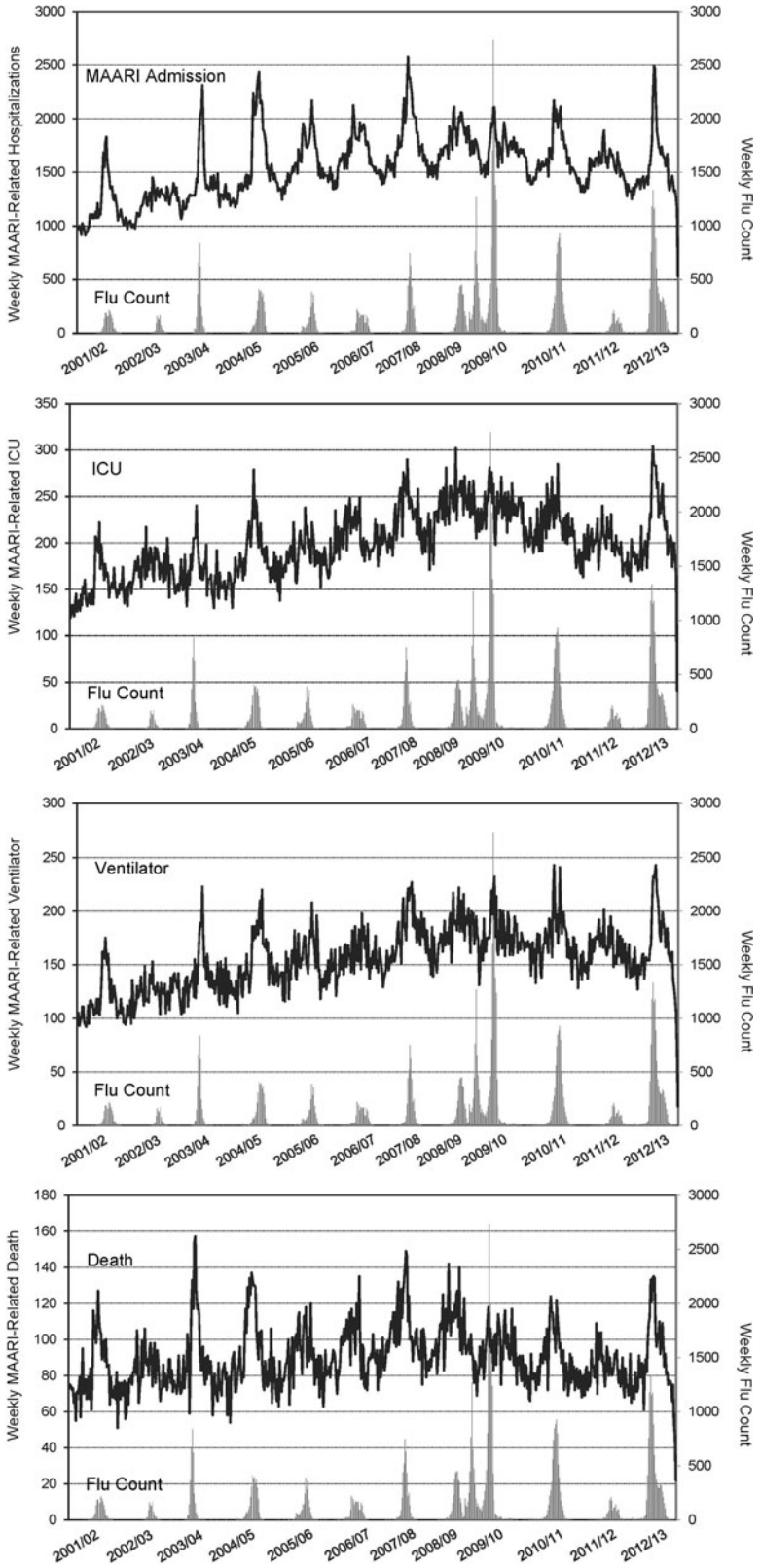

Fig. 1. Plots of the four study outcomes[a] and weekly counts of positive influenza tests[b] in the Maryland area.

[a] Study outcomes consist of medically attended acute respiratory illness (MAARI) related hospitalizations, intensive care unit admission, mechanical ventilation, and death.

[b] Positive influenza test data obtained from the United States Center for Disease Control and Prevention interactive website for Region 3 [17].

Table 3. *Spearman's correlation coefficients (CCs)*[a] *of the four MAARI-related*[b] *weekly study outcomes in adults compared with weekly influenza counts within the influenza outbreak period*

Age groups	Total flu count	H1 count	H3 count	B count
All adults				
Hospitalization	**0·545**	0·245	**0·359**	**0·327**
ICU admission	**0·598**	**0·501**	0·188	0·335
Mechanical ventilation	**0·584**	**0·384**	**0·381**	**0·349**
Death	**0·382**	−0·040	0·274	0·238
18 to <50 years				
Hospitalization	**0·456**	0·213	0·093	0·099
ICU admission	**0·563**	**0·388**	0·087	0·149
Mechanical ventilation	**0·487**	**0·317**	0·201	0·099
Death	0·066	−0·081	−0·112	−0·171
50 to <65 years				
Hospitalization	**0·594**	**0·453**	**0·332**	**0·318**
ICU admission	**0·457**	**0·522**	0·174	0·325
Mechanical ventilation	**0·494**	**0·510**	0·327	0·306
Death	0·282	0·303	0·213	0·146
⩾65 years				
Hospitalization	**0·447**	0·090	**0·509**	**0·404**
ICU admission	**0·476**	0·316	0·227	0·320
Mechanical ventilation	**0·453**	0·119	**0·420**	**0·338**
Death	0·328	−0·156	**0·307**	**0·304**

[a] Bold CC denote moderate-to-high elevation.
[b] MAARI is medically attended acute respiratory illness.

group of patients 18 to <50 years of age. Moreover, this younger age group had a trend towards similar but numerically higher RRs for three of the four outcomes (hospitalization, ICU, death) compared with the two older groups. In addition, numerically higher RRs were observed for the category death *vs.* the other three outcomes for all age groups combined and each of the three age subgroups.

DISCUSSION

The results of this study demonstrated that significant surges in all four study outcomes occur simultaneously with influenza outbreaks almost every influenza season in adults. These results confirm multiple previous reports of increases of the individual outcome components investigated in this study associated with influenza outbreaks [1, 2, 6–18]. The present study is unique in that it provides quantitative assessments of the association of all four outcomes to influenza outbreaks for 12 consecutive years for nearly one million patients, and estimated RR of the outcomes of interest during the IOP compared against the NIOP.

Analyses of the present study's data reaffirm previous publications on the impact of age or virus type on advanced medical outcomes related to influenza outbreaks [19, 20]. A/H1N1 viruses are associated with greater use of advanced medical care in the two younger age groups of 18 to 64 years compared with the group 65 years and older, but A/H3N2 and B viruses were associated with higher CCs for the oldest group aged 65 years of age or older.

Second, illnesses due to influenza B have been considered to be milder than illnesses caused by influenza A viruses for uncomplicated influenza infections [18, 21]. However, the present study corroborates more recent findings that hospitalized patients with influenza B have similar severities in patients hospitalized with influenza A viruses with regard to ICU admission, mechanical ventilation or inpatient deaths [22–24].

Third, younger adults are less frequently hospitalized with influenza infection [7, 18]. However, data reported in the present study support a previous study [2] showing that once hospitalized, younger adults aged 18 to <65 years, and even adults younger than 50 years of age experience similar severity of illness in terms of the percentage of hospital admissions resulting in an ICU admission, mechanical ventilation or death when compared with adults 65 years of age or older. A possible explanation for this observation is that clinicians may more frequently hospitalize older individuals with a less severe respiratory illness than young adults because of increased risk factors [25].

There are limitations in this study. First, it was not possible to directly identify the pathogens in the study population that were associated with increases in the four study outcomes. However, linking the surges in MAARI-related study outcomes to influenza surveillance suggests that influenza illness was an important factor for these outcome increases. Second, HHS Region 3 influenza virus surveillance data may not exactly match the quantity and type of influenza viruses circulating specifically in Maryland. Third, data from Maryland hospitals may not reflect influenza outcomes in other states or regions because of possible geographic and demographic differences. Finally, there are confounders that could have an impact on the estimation of the CCs and RRs, but could not be adequately evaluated by using large administrative or observational databases. However,

linking surges of MAARI-related study outcomes to influenza surveillance suggest that influenza illness was at least an important factor for these medical resource and outcome increases.

The advantage of using the State of Maryland HSCRC data for the analyses was that it included a broad variety of hospitals [12]. Maryland acute-care hospitals included community, teaching, and public hospitals that differ in their floor and ICU bed capacity and may differ in their patient populations as well as clinician practices. This hospital variety may more realistically mirror the broad spectrum of medical care delivered to patients with more severe influenza illness.

SUMMARY

The results of this study reaffirm that surges in advanced medical support and in-hospital deaths during influenza outbreaks each season were common over a 12-year period of time. These observations strongly support recommendations that the development of more effective vaccines should be a high priority [26] and that new, more effective therapeutic agents for influenza must be found to decrease the mortality, morbidity and cost of influenza epidemics.

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DECLARATION OF INTEREST

All the authors declare that there are no conflicts of interest.

ETHICAL APPROVAL

The University of Maryland School of Medicine Institutional Review Board has reviewed and approved this study. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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