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_____ _____

Donghwan H. Chang, MD Date

Trends in U.S. Hospitalizations and Inpatient Deaths
from Pneumonia and Influenza, 1996-2011

By

Donghwan H. Chang

Degree to be awarded: MPH

Department of Epidemiology

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Saad B. Omer
Committee Chair

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By

Donghwan H. Chang

Bachelor of Korean Medicine
Kyung Hee University
2013

Thesis Committee Chair: Saad B. Omer, MBBS, MPH, PhD, FIDSA

An abstract of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology

2015

Abstract

Trends in U.S. Hospitalizations and Inpatient Deaths
from Pneumonia and Influenza, 1996-2011

By Donghwan H. Chang

Background To reduce excessive morbidity and mortality of pneumonia and influenza (P&I), the Advisory Committee on Immunization Practices (ACIP) has recommended the use of 23-valent pneumococcal polysaccharide vaccine (PPSV23), 7-valent pneumococcal conjugate vaccine (PCV7), and 13-valent pneumococcal conjugate vaccine (PCV13) over the past two decades, as well as incrementally expanded the target group for annual influenza vaccination of healthy persons, to ultimately include all persons >= 6 months of age without contraindications as of the 2010-11 influenza season. There has not been a published study of trends in P&I hospitalizations in the U.S since 2002.

Methods Using the Nationwide Inpatient Sample, we constructed and analyzed annual and monthly rates of P&I hospitalization and inpatient death from 1996 to 2011, adjusted for sex and age. P&I hospitalizations were defined as a principal diagnosis of P&I, or a principal diagnosis of sepsis or respiratory failure, accompanied by a secondary diagnosis of P&I. Rate differences, and reductions in P&I hospitalizations and inpatient deaths in absolute and relative terms were calculated to summarize the changes during the study period.

Results Overall rates of P&I hospitalizations and inpatient deaths declined by 26 per 100,000 (5%) and by 5.7 per 100,000 (13%), respectively. This translates to 81,000 fewer P&I hospitalizations and 17,800 fewer P&I inpatient deaths in 2011 compared to 1996. The rates of P&I hospitalization dropped the most among children aged <2 (50% decrease; absolute decrease of 638 per 100,000), followed by seniors aged 65+ (7% decrease; absolute decrease of 167 per 100,000). The rates of P&I inpatient death declined the most among seniors aged 65+ (19% decrease; absolute decrease of 52.0 per 100,000).

Conclusions In this nationally representative study, P&I hospitalizations and inpatient deaths decreased in the U.S. between 1996 and 2011. While it is difficult to attribute these changes directly to specific vaccines in this era, overall epidemiologic changes in P&I hospitalizations and inpatient deaths are likely to be due to the introduction of PCV7, and the expansion of the target group for annual influenza vaccination of healthy persons.

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Chapter I: Background

Pneumonia and Influenza

Pneumonia and influenza (P&I) are a source of substantial morbidity and mortality in the United States (U.S.) and worldwide.[1,2] Annually, around 1 million patients are hospitalized for 5.2 days on average, and about 70,000 deaths occur, due to P&I.[3-6] Average rate of P&I death from 1999 to 2006 was 21.5 per 100,000 (range: 17.8-23.7),[7] and seniors aged 65+ accounted for 90% of all P&I deaths,[8] with an average death rate of 218 per 100,000 (range: 189-237).[7]

Pneumonia, defined as an infection of the pulmonary parenchyma, can be caused by various pathogens: namely, *Streptococcus pneumoniae, Mycoplasma pneumoniae, Haemophilus influenza, Streptococcus aureus, Moraxella catarrhalis*, and respiratory viruses, which include influenza viruses, adenoviruses, respiratory syncytial viruses (RSV), and parainfluenza viruses.[9,10]

Among the pathogens, *S pneumoniae,* gram-positive and lancet-shaped bacteria, were known as a major factor of substantial morbidity and mortality for more than a century, which led to the development of pneumococcal vaccines.[11] Although there are more than 90 serotypes discovered, about 60% of invasive pneumococcal diseases worldwide were attributable to the 10 most common serotypes.[11] Polysaccharide capsules were found to be an important factor determining the virulence, based on observation that organisms with polysaccharide capsules were pathogenic to human, while organism without polysaccharide capsules were not pathogenic.[11]

Pneumococcal pneumonia is characterized by an abrupt onset of fever, and rigors or shaking chills, with an incubation period of 1-3 days.[12] Other common symptoms include pleuritic chest pain, productive cough, dyspnea, tachypnea, and hypoxia.[12] Pneumococcal infection can lead to bacteremia, or meningitis, the case fatality of which are higher than 20%.[12] Those who are immunocompromised, or with decreased immune function, who are asplenic or hyposplenic, who have chronic heart, pulmonary, liver, or renal diseases, and who smoke are considered to be at increased risk of invasive pneumococcal diseases.[12]

Influenza is a viral respiratory illness caused by influenza virus, a single-stranded RNA virus within the orthomyxoviridae family.[12] The virus is categorized into 3 types: A, B, and C. Type A influenza virus is further subcategorized according to its surface antigens, hemagglutinin (H) and neuraminidase (N). There are three types of hemagglutinin that attach to human cells (H1, H2, H3), and there are two types of neuraminidase that penetrate into cells (N1, N2) [12].

Surface antigens undergo changes over time, through point mutations, or the exchange of gene segments. According to the extent of the antigenic changes in influenza virus, these phenomena are named as antigenic drift, or antigenic shift. Antigenic drift consists of minor changes in surface antigens, caused by point mutations in a gene segment. Though the subtype remains the same, antigenic drift has a potential to cause an epidemic, since the acquired immunity from previous exposures cannot function as effectively [12]. Antigenic shift means the appearance of new subtype, resulting from the exchange of gene segments,

which has a potential to cause a pandemic. The more antigenic changes usually imply the stronger impact upon morbidity [12]. Historically overall burden of influenza was higher in the seasons when strain A(H3N2) predominantly circulated, compared with the seasons when strain A(H1N1) or strain B was dominant [13].

Influenza follows respiratory transmission, invading and replicating in the epithelial cells of trachea and bronchi. As influenza virus further replicates, host cells are disintegrated. Shedding virus is detected in respiratory secretions for 5-10 days, and viraemia, the presence of a virus in the blood stream, seldom occurs [12]. Incubation period is typically 2 days, which may range from 1 to 4 days. Common symptoms are fever, cough, myalgia, sore throat, rhinorrhea (runny nose), and headache, however the severity of illness is up to one's past immunologic history, i.e. previous exposure to similar antigen. The illness from influenza can develop pneumonia, most commonly secondary bacterial pneumonia. Primary influenza viral pneumonia is uncommon, yet its case fatality rate is high. Other complications include Reye syndrome and myocarditis.

Typically in North America, influenza is seasonal, with influenza positivity rising between the 42-44th weeks, peaking around the 6-8th weeks, and maintaining a low level between 32-34th weeks of a given year [14].

Pneumococcal vaccines

There are two types of pneumococcal vaccines approved in the U.S., pneumococcal polysaccharide vaccine (PPSV) and pneumococcal conjugate

vaccine (PCV). A 14-valent PPSV (PPSV14) was first licensed in the U.S. in 1977, and a 23-valent PPSV (PPSV23) was licensed in 1983.[12] To reduce the burden of P&I, the Advisory Committee on Immunization Practices (ACIP) recommended the use of PPSV23 for seniors aged 65+, 7-valent PCV (PCV7) for children aged <2 and children aged 2-4 at increased risk in 2000, and 13-valent PCV (PCV13) for children aged <5 and children 6 years old with underlying medical conditions.[15-17]

Influenza vaccines

There are two types of influenza vaccines approved in the U.S., trivalent inactivated influenza vaccine (IIV3) and live attenuated vaccine (LAIV). In U.S., IIV3 has been available since 1940s, and LAIV became available in 2003 [12]. IIV3 is injected either intramuscular or intradermal, and LAIV is intranasally admitted. Unlike IIV3, LAIV is potent of transmitting the vaccine virus to the administered, however there is no such case reported in the U.S.[12].

As an effort to prevent and control influenza, the ACIP annually releases a recommendation on influenza vaccination for the upcoming influenza season. The policy for annual influenza vaccination for healthy persons changed from targeting individuals aged 65+ only to universal immunization over the past 2 decades.

The ACIP's initial move towards universal influenza vaccination for healthy persons, i.e. lowering the age of annual influenza vaccination for healthy persons from 65 to 50 years, was triggered by the recommendation from the American Academy of Family Physicians (AAFP) in 1999, to reduce the disease

burden in terms of outpatient visits, hospitalizations, working days lost, and health care costs [18].

Children aged older than 6 months to less than 2 years were introduced to the target group during the 2004-05 season. The universal immunization policy for healthy persons, recommending influenza vaccination for all healthy persons aged ≥6 months without any contraindications, began from the 2010-11 season, after the age groups of 2-4, 5-18, and 19-49 years were consecutively added to the target group at two-year intervals.

Study rationale, and objectives

A lot of previous studies focused on evaluating the impact of a specific vaccine. The effectiveness of pneumococcal vaccines were measured by examining the trends in hospitalizations of pneumococcal infection-specific diagnosis codes,[19-22] and the effectiveness of influenza vaccines were estimated in terms of prevented cases, hospitalizations, and deaths, or by analyzing the trends in influenza-associated hospitalizations and deaths, calculated based on viral surveillance data.[8,23-25] However, given the substantial evidence of predisposition to pneumococcal infection with preceding influenza infection, there may be broader epidemiologic changes in the burden of P&I, that have not yet been documented.[26,27]

In the light of the aforementioned changes in vaccine recommendations, there has not been a published study of an analysis of trends in P&I hospitalizations in the U.S since 2002.[3,28-30] Therefore, in this study, we

investigated epidemiologic trends in P&I hospitalizations and inpatient deaths from 1996 to 2011 in the U.S.

Chapter II: Manuscript

Introduction

Pneumonia and influenza (P&I) are a source of substantial morbidity and mortality in the United States (U.S.) and worldwide.[1,2] Annually, around 1 million patients are hospitalized for 5.2 days on average, and about 70,000 deaths occur, due to P&I.[3-6] Average rate of P&I death from 1999 to 2006 was 21.5 per 100,000 (range: 17.8-23.7),[7] and seniors aged 65+ accounted for 90% of all P&I deaths,[8] with an average death rate of 218 per 100,000 (range: 189-237).[7]

To reduce the burden of P&I, the Advisory Committee on Immunization Practices (ACIP) recommended the use of 23-valent pneumococcal polysaccharide vaccine (PPSV23) for seniors aged 65+ in 1997,[17] 7-valent pneumococcal conjugate vaccine (PCV7) for children aged 2-23 months, and children aged 24-59 months at increased risk in 2000,[16] and 13-valent pneumococcal conjugate vaccine (PCV13) for children aged 2-59 months, and children aged 60-71 months with underlying medical conditions in 2010,[15] as well as incrementally expanded the target group for annual influenza vaccination of healthy persons, from all persons aged 65+ years to ultimately include all persons >= 6 months of age without contraindications as of the 2010-11 influenza season.[31-35]

In the light of these changes in vaccine recommendations, there has not been a published study of an analysis of trends in P&I hospitalizations in the U.S since 2002.[3,28-30] Therefore, in this study, we investigated epidemiologic trends in P&I hospitalizations and inpatient deaths from 1996 to 2011 in the U.S.

Methods

Study population

The NIS is the largest all-payer publicly available database of aggregated hospital discharge records, funded by the Agency for Healthcare Research and Quality (AHRQ) [36]. The NIS is comprised of approximately 8 million hospitalizations annually from about 1,000 hospitals. Time trend analysis is recommended from 1993, when the coverage of the sampling frame exceeded 50%.[37] We analyzed the NIS data from 1996 to 2011, during which the sampling coverage steadily increased from about 60%. As of 2011, the NIS represented over 97% of all U.S. hospitalizations involving 46 states.[38] The NIS has a complex sampling design, employing a community hospital as a primary sampling unit (PSU), and sampling probabilities are proportional to the size of each cluster, i.e. the number of PSUs, with an approximate 20% sampling rate.[38,39]

Definition of hospitalizations for pneumonia and influenza

Patients with a primary diagnosis of *Pneumonia and Influenza* (*International Classification of Disease, 9th Revision, Clinical Modification,* ICD-9-CM; 480.xx-488.xx) at the time of discharge were included in the study. To account for alternative coding options, and temporal trends in diagnostic coding practice, patients with a principal diagnosis of sepsis (038.xx, 995.91, 995.92, 785.52), or respiratory failure (518.81, 518.82, 518.84, 799.1), followed by a secondary diagnosis of P&I were also included.[40]

Data analysis methods

Monthly, and annual U.S. nationwide estimates of P&I hospitalizations and inpatient deaths were calculated for six pre-determined age groups (<2, 2-4, 5-17, 18-49, 50-64, 65+), stratified by sex. These estimates were converted to rates, divided by mid-year (July 1st) national population estimates from the U.S. Census Bureau. Obtained crude rates were then adjusted for sex and age to the 2011 population to construct time series. Since the NIS comprised discharge data rather than admission data, admission year was inferred to the best possible extent, based on admission month, length of hospital stay, and year of discharge.

Rate differences, absolute and relative (per cent) reductions in hospitalizations and inpatient deaths were calculated using the method of Griffin et al.[22] The variance of the rate differences were the sum of the variances of the rates compared, and relative reductions in rates were derived from the rate differences. Absolute reductions in hospitalizations and inpatient deaths were calculated applying the estimated rate differences to the population in 2011, to summarize the changes during the whole study period, from 1996 through 2011. All analyses were performed using SAS 9.4 (Cary, NC, USA).

Disclosures

This study was exempt for review, not meeting the criteria of research involving human subjects nor clinical investigation, determined by the Emory University institutional review board.

Results

Between 1996 and 2011, there was a total of 23,858,402 P&I hospitalizations, and 1,782,794 P&I inpatient deaths in the U.S., which accounted for 4.0% and 13.6% of all hospitalizations and inpatient deaths in the U.S., respectively. The proportions of P&I hospitalizations among all hospitalizations were on average 4.6% among males (range: 4.3%-5.1%) and 3.5% among females (range: 3.2%-3.9%) throughout the study period.

Overall rates of P&I hospitalizations and inpatient deaths decreased from 528 to 519 per 100,000, and 44 to 38 per 100,000, respectively (Figure 1A, 1C). Among children aged <2, both the rates of P&I hospitalization and inpatient death halved from 1,280 to 641 per 100,000, and from 3.2 to 1.6 per 100,000, respectively (Figure 1B, 1D). Among seniors aged 65+, the rates of P&I hospitalization and inpatient death moderately decreased from 2,381 to 2,214 per 100,000, and from 269 to 217 per 100,000, respectively. Among those aged 50-64, both the rates of P&I hospitalization and inpatient death increased, from 480 to 542 per 100,000, and from 30 to 35 per 100,000, respectively.

Seasonal peaks were observed both in P&I hospitalizations and inpatient deaths (Figure 2A-2D). While all age groups demonstrated seasonality in P&I hospitalizations (Figure 2B), seasonality of P&I inpatient deaths were observable among adult age groups only (18-49, 50-64, 65+) (Figure 2D). Monthly rates of P&I inpatient death among children age groups (<2, 2-4, 5-17) heavily fluctuated with rates below 1 per 100,000 (Figure S2C).

Overall rates of P&I hospitalization were similar in both sexes, with rate ratios close to 1.00, while overall rates of P&I inpatient death among males were

generally higher than females throughout the study period (Figures 3A, 3C). In all age groups except those aged 18-49, the rates of P&I hospitalization among males were higher than females, the geometric means of rate ratios ranging from 1.03 to 1.30 (Figure 3B). Among adult age groups (18-49, 50-64, 65+), the rates of P&I inpatient death among males were consistently higher than females, with geometric means of rate ratios ranging from 1.21 to 1.32 (Figure 3D). The rate ratios of P&I inpatient death among children age groups (<2, 2-4, 5-17) fluctuated around 1.00.

There was a total of 81,000 (5%) fewer P&I hospitalizations and 17,800 (13%) fewer P&I inpatient deaths in 2011, compared to the rates in 1996 (Table 1). P&I hospitalizations decreased by 51,000 (50%) and 69,000 (7%), among those aged <2 and 65+, respectively, and increased by 15,000 (8%) and 38,000 (13%) among adults aged 18-49 and 50-64, respectively. P&I inpatient deaths among seniors aged 65+ decreased by 21,500 (19%), and increased by 1,100 (15%) and 2,800 (19%) among adults aged 18-49 and 50-64, respectively. Generally, there were bigger reductions among males in the rates of P&I hospitalization and inpatient death than among females.

Discussion

Overall, the burden of P&I hospitalizations and inpatient deaths in the U.S. decreased in 2011 compared to 1996, most notably at the extremes of age groups (<2, 65+). However, total reductions, both in hospitalizations and inpatient deaths due to P&I, were offset by moderate increases among those aged 18-49 and 50-64 since 2004. Due to the low rates of P&I inpatient death among children aged <2, their contribution to total reductions was minute despite 50% reduction in relative terms.

There appeared to be no gender difference in the overall rates of P&I hospitalization, despite higher rates among males in many age groups. Lower rates of P&I hospitalizations among males of those aged 18-49, which comprise about 45% of total U.S. population, balanced out with higher rates in other age groups, and masked gender gaps in P&I hospitalization rates. Higher rates of P&I inpatient death among males of adult age groups (18-49, 50-64, 65+) resulted in higher overall rates, and no distinctive pattern could be identified in the rate ratios of P&I inpatient death among children due to low and fluctuating rates.

The rates of P&I hospitalization and inpatient death may be reflecting the activity of both pneumococcus and influenza. The rates of P&I hospitalization and inpatient death, particularly among those aged <2 and 65+, significantly dropped in 2000 with the introduction of PCV7. The declinations in the rates of P&I hospitalization from 2002 to 2008, which were moderate among children aged <2, and modest among children aged 2-4, may be chiefly attributable to PCV7, when the coverage of which among children aged 19-35 months soared up

from 40% to 80% during this period.[41] Also, the coverage of PPSV23 among seniors aged 65+ was 42% in 1997, passed 50% in 2000, and steadily rose up to 62% in 2011.[41]

When influenza seasons were mild in 2001 and 2007,[42,43] the rates were slightly lower than adjacent years. In 2003, 2005, and 2008, when influenza seasons were severe with poorly matching vaccine strains with circulating strains, and in 2009 when H1N1 pandemic occurred,[44-48] the rates were higher than the rates in the years nearby. The declining trends in the rates of P&I hospitalization and inpatient death since 2004 may be partially ascribable to the increased coverage of influenza vaccination, in addition to PCV7. The coverage of influenza vaccination among children (6 mo – 17 yr) rapidly rose from 31% in 2007 to 57% in 2011.[49] There were also steady increases in coverage, from 15% to 29% among adults aged 18-49, and from 33% to 43% among adults aged 50-64, from 2005 to 2011.[50,51] The coverage of seniors aged 65+ remained stable around the average of 68% (range: 65-70%) during the same period (2005-2011).

On the other hand, increasing trends in both the rates of P&I hospitalization and inpatient death among adults aged 18-49 and 50-64 from 2004 are difficult to explain. Hospitalization rates for chronic obstructive pulmonary disease (COPD) modestly decreased throughout the study period,[52-54] and smoking rate fell from 25% in 1997 to 21% in 2004, and plateaued until 2009. Respiratory syncytial virus (RSV) mainly afflicts children, and the rates of RSV-associated hospitalization were low and stable among those aged 5-49 (<2 per 100,000), and halved among those aged 50-64 from 14.6 to 7.3 per 100,000 from 1996 to 2008.[25]

Many studies focused on evaluating the impact of individual vaccines, i.e. pneumococcal vaccines, or influenza vaccines. The effectiveness of pneumococcal vaccines were measured by examining the trends in incidences of invasive pneumococcal disease, or hospitalizations for pneumococcus-related diagnoses,[19-22,55-58] and the effectiveness of influenza vaccines were estimated in terms of prevented cases, hospitalizations, and deaths, or by analyzing the trends in influenza-associated hospitalizations and deaths, calculated based on viral surveillance data.[8,23-25] In this study, we tried to capture broader epidemiologic changes in health burden by looking at P&I collectively, given the substantial evidence of predisposition to pneumococcal infection with preceding influenza infection.[26,27]

The main limitation of our study is that the NIS did not contain information on the vaccination status of each patient, nor whether diagnoses were laboratory-confirmed. Although we were unable to investigate the effects of vaccination at an individual level, our findings reassure that overall P&I hospitalizations and mortality have declined at a national level, in line with previous studies.[19,22,55-58] Another limitation is that we could not provide explanations for increasing trends in P&I hospitalizations and inpatient deaths among adults aged 18-49 and 50-64, despite decreased or stable other risk factors of pneumonia, and increased coverage of influenza vaccination.

Conclusion

In this nationally representative study, P&I hospitalizations and inpatient deaths decreased in the U.S. between 1996 and 2011. While it is difficult to attribute these changes directly to specific vaccines in this era, overall epidemiologic changes in P&I hospitalizations and inpatient deaths are likely to be due to the introduction of PCV7, and the expansion of the target group for annual influenza vaccination of healthy persons. We believe that the burden can be further reduced, considering the relatively low coverage of influenza vaccination, 32% among adults aged 18-49 and 45% among adults aged 50-64 as of the 2013-14 influenza season, and varying coverage across states ranging 40%-70% among children, and 30%-50% among adults.[49,50]

Chapter III: Summary, Public Health Implications, Possible Future Directions

Overall, the burden of P&I hospitalizations and inpatient deaths in the U.S. decreased in 2011 compared to 1996, most notably at the extremes of age groups (<2, 65+). However, total reductions, both in hospitalizations and inpatient deaths due to P&I, were offset by moderate increases among those aged 18-49 and 50-64 since 2004. Due to the low rates of P&I inpatient death among children aged <2, their contribution to total reductions was minute despite 50% reduction in relative terms.

While it is difficult to attribute these changes directly to specific vaccines in this era, overall epidemiologic changes in P&I hospitalizations and inpatient deaths are likely to be due to the introduction of PCV7, and the expansion of the target group for annual influenza vaccination of healthy persons.

Universal immunization policy has proven itself to be an effective and powerful measure to relieve the burden of vaccine-preventable diseases, as documented in many studies.[59-65] Universal influenza immunization program (UIIP) implemented in Ontario, Canada, were found to have led to substantial reductions in influenza-associated hospitalizations and mortality, compared to targeted immunization practices for specific population in other regions in Canada.[64] Universal Varicella Vaccination programme, regionally implemented in Italy in 2003, and become national in 2015, reduced the incidences and hospitalizations for varicella.[60,61] In Uruguay, the rates of CAP and pneumococcal CAP incidence rapidly and significantly declined, following the introduction of PCV7 and PCV13 in its routine immunization schedule.[63]

Yet universal vaccination is not always the best way among possible interventions. A study conducted in Greece regarding universal vaccination policy against hepatitis A revealed that there was no substantial change, or reduction in the annual number of reported cases despite the implementation of universal vaccination program, and concluded that it would be more cost-effective to vaccinate high risk groups, to educate, and to enhance disease control measures.[66] Also, Navarro-Illana et al. pointed out concerns from an ethical point of view, that, in case of human papilloma virus (HPV) vaccination, attenuating the fear of developing cancer could lead to an increase in risky behaviors, while the medical advantages of vaccination still uphold.[67]

Next steps would include improving effectiveness, continuously measuring the effectiveness/utility, annually as well as periodically, and improving coverage of pneumococcal and influenza vaccines. In case of influenza vaccine, year-to-year variability in the effectiveness of vaccines has been recognized, primarily depending on whether the strains included in the vaccine matched the circulating strains or not, thus inducing uncertainty regarding the utility of influenza vaccines on overall morbidity and mortality.[68-70]

The utility of pneumococcal and influenza vaccination programmes should be kept evaluated, with annual and/or periodic assessment of the effectiveness of vaccines, directly by examining the trends in incidence, medical attendance, hospitalization, and mortality, and indirectly by estimating the prevented fractions and numbers in those, as done in the previous studies.[8,19-25]

It is deemed that the burden of P&I can be further reduced, considering the relatively low coverage of influenza vaccination, 32% among adults aged 18-

49 and 45% among adults aged 50-64 as of the 2013-14 influenza season, and varying coverage across states ranging 40%-70% among children, and 30%-50% among adults.[49,50]

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Appendices

Figures

Figure Legends

Figure 1. Sex and Age-adjusted Annual Rates of Hospitalization and Inpatient Death from Pneumonia and Influenza in U.S. from 1996 to 2011

Panel A shows annual rates of hospitalization for pneumonia and influenza.

Panel B shows annual rates of hospitalization for pneumonia and influenza, according to age group.

Panel C shows annual rates of inpatient death from pneumonia and influenza.

Panel D shows annual rates of inpatient death from pneumonia and influenza, according to age group.

Panel E shows recommended age groups for annual influenza vaccination among healthy persons by the Advisory Committee on Immunization Practices (ACIP).

* Children under 6 months old were not included in the recommendation for influenza vaccination.

** Arrows indicate newly introduced age groups to the recommendation for annual influenza vaccination, or a recommended vaccine (23-valent pneumococcal polysaccharide pneumococcal vaccine, PPSV23; 7-valent pneumococcal vaccine, PCV7; trivalent inactivated influenza vaccine, IIV3).

Figure 2. Sex and Age-adjusted Monthly Rates of Hospitalization and Inpatient Death from Pneumonia and Influenza in U.S. from 1996 to 2011

Panel A shows monthly rates of hospitalization for pneumonia and influenza.

Panel B shows monthly rates of hospitalization for pneumonia and influenza, according to age group.

Panel C shows monthly rates of inpatient death from pneumonia and influenza.

Panel D shows monthly rates of inpatient death from pneumonia and influenza, according to age group.

* Rates were adjusted for sex and age to the population in 2011.

Figure 3. Rate Ratio of Hospitalizations and Inpatient Deaths from Pneumonia and Influenza, Male vs Female

Panel A shows the rate ratios of hospitalization, male vs female.

Panel B shows the rate ratios of hospitalization according to age group, male vs female.

Panel C shows the rate ratios of inpatient death, male vs female.

Panel D shows the rate ratios of inpatient death according to age group, male vs female.

* Rate ratios (Y-axes) are in logarithmic scale.

Figure S1. Annual Rates of Hospitalization and Inpatient Death from Pneumonia and Influenza in U.S. from 1996 to 2011, According to Age Group and Sex

Panel A shows annual rates of hospitalization for pneumonia and influenza among children, stratified by sex.

Panel B shows annual rates of hospitalization for pneumonia and influenza among adults, stratified by sex.

Panel C shows annual rates of inpatient death from pneumonia and influenza among children, stratified by sex.

Panel D shows annual rates of inpatient death from pneumonia and influenza among adults, stratified by sex.

Panel E shows recommended age groups for annual influenza vaccination among healthy persons by the Advisory Committee on Immunization Practices (ACIP).

* Children under 6 months old were not included in the recommendation for influenza vaccination.

** Arrows indicate newly introduced age groups to the recommendation for annual influenza vaccination, or a recommended vaccine (23-valent pneumococcal polysaccharide pneumococcal vaccine, PPSV23; 7-valent pneumococcal vaccine, PCV7; trivalent inactivated influenza vaccine, IIV3).

Figure S2. Monthly Rates of Inpatient Death for Pneumonia and Influenza in U.S. from 1996 to 2011, According to Sex and Age Group

Panel A shows monthly rates of hospitalization for pneumonia and influenza among children, stratified by sex.

Panel B shows monthly rates of hospitalization for pneumonia and influenza

among adults, stratified by sex.

Panel C shows monthly rates of inpatient death from pneumonia and influenza among children, stratified by sex.

Panel D shows monthly rates of inpatient death from pneumonia and influenza among adults, stratified by sex.

† Abbreviations: M, Male; F, Female

Figure 1

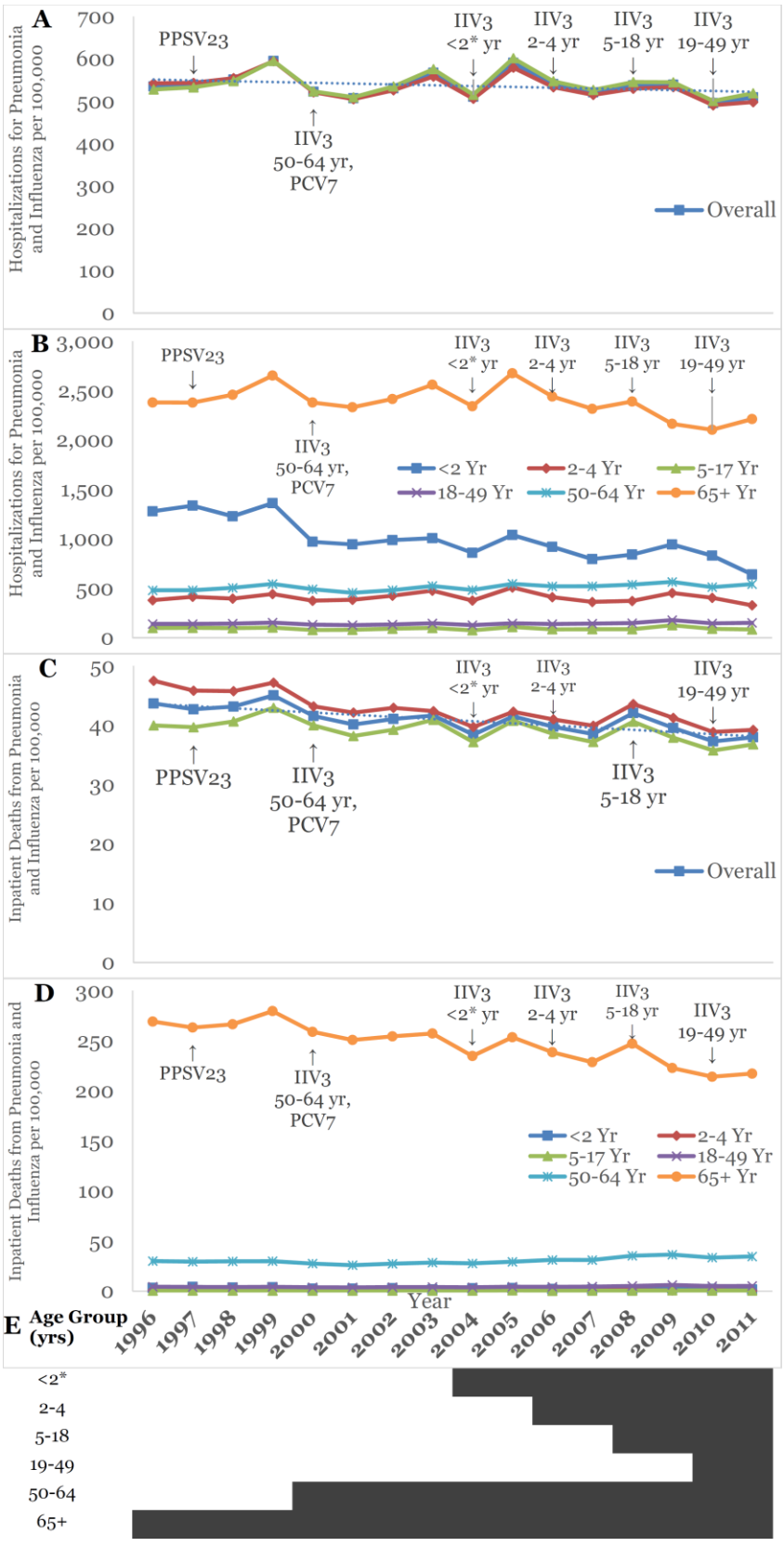

A
Hospitalizations for Pneumonia and Influenza per 100,000
700
600
500
400
300
200
100
0
PPSV23
IIV3 50-64 yr, PCV7
IIV3 <2* yr
IIV3 2-4 yr
IIV3 5-18 yr
IIV3 19-49 yr
Overall
B
Hospitalizations for Pneumonia and Influenza per 100,000
3,000
2,500
2,000
1,500
1,000
500
0
PPSV23
IIV3 50-64 yr, PCV7
IIV3 <2* yr
IIV3 2-4 yr
IIV3 5-18 yr
IIV3 19-49 yr
<2 Yr
2-4 Yr
5-17 Yr
18-49 Yr
50-64 Yr
65+ Yr
C
Inpatient Deaths from Pneumonia and Influenza per 100,000
50
40
30
20
10
0
PPSV23
IIV3 50-64 yr, PCV7
IIV3 <2* yr
IIV3 2-4 yr
IIV3 5-18 yr
IIV3 19-49 yr
Overall
D
Inpatient Deaths from Pneumonia and Influenza per 100,000
300
250
200
150
100
50
0
PPSV23
IIV3 50-64 yr, PCV7
IIV3 <2* yr
IIV3 2-4 yr
IIV3 5-18 yr
IIV3 19-49 yr
<2 Yr
2-4 Yr
5-17 Yr
18-49 Yr
50-64 Yr
65+ Yr
Year
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
E
Age Group (yrs)
<2*
2-4
5-18
19-49
50-64
65+

Figure 2

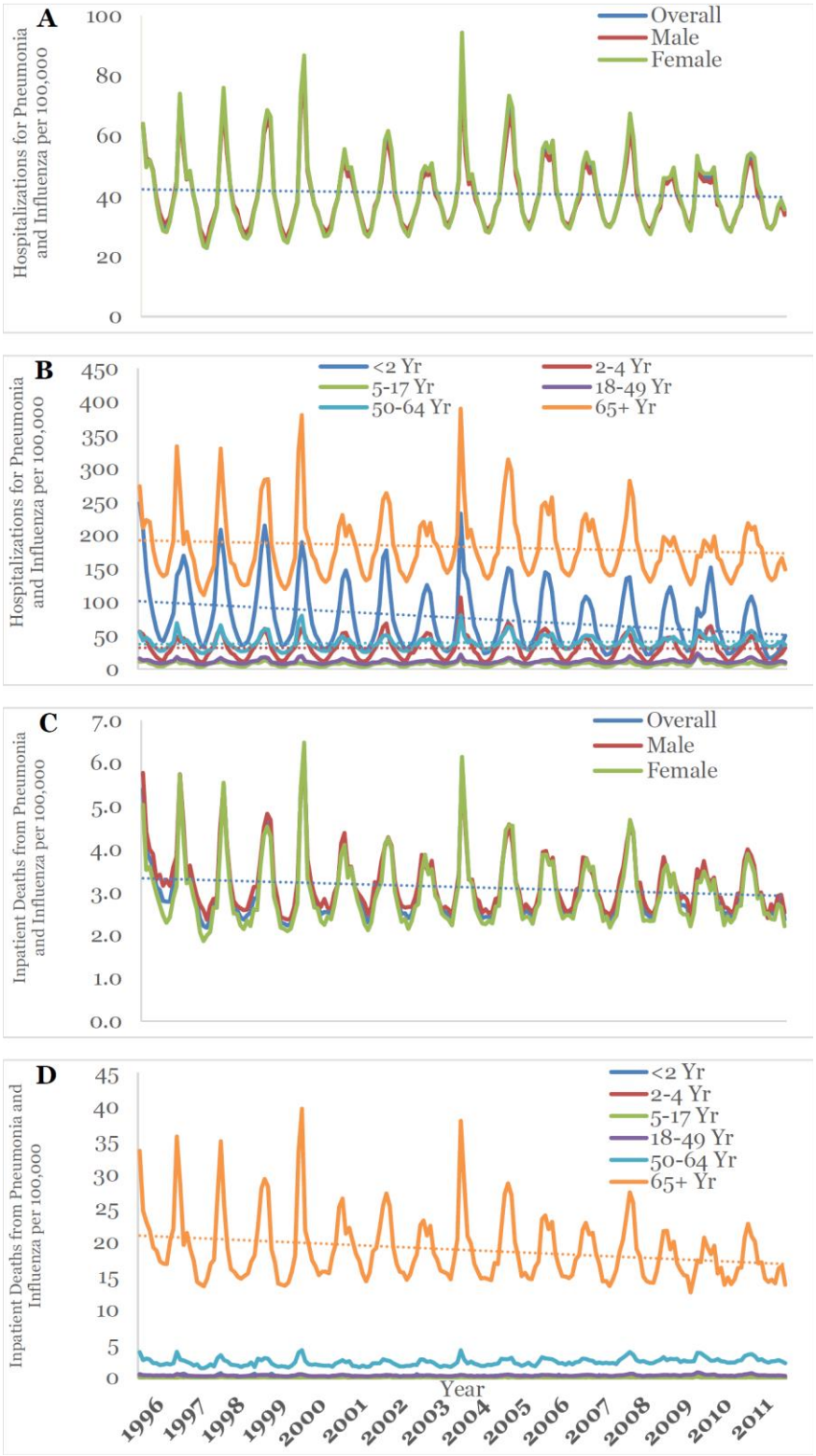

A
Hospitalizations for Pneumonia and Influenza per 100,000
100
80
60
40
20
0
Overall
Male
Female
B
Hospitalizations for Pneumonia and Influenza per 100,000
450
400
350
300
250
200
150
100
50
0
<2 Yr
2-4 Yr
5-17 Yr
18-49 Yr
50-64 Yr
65+ Yr
C
Inpatient Deaths from Pneumonia and Influenza per 100,000
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Overall
Male
Female
D
Inpatient Deaths from Pneumonia and Influenza per 100,000
45
40
35
30
25
20
15
10
5
0
<2 Yr
2-4 Yr
5-17 Yr
18-49 Yr
50-64 Yr
65+ Yr
Year
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011

Figure 3

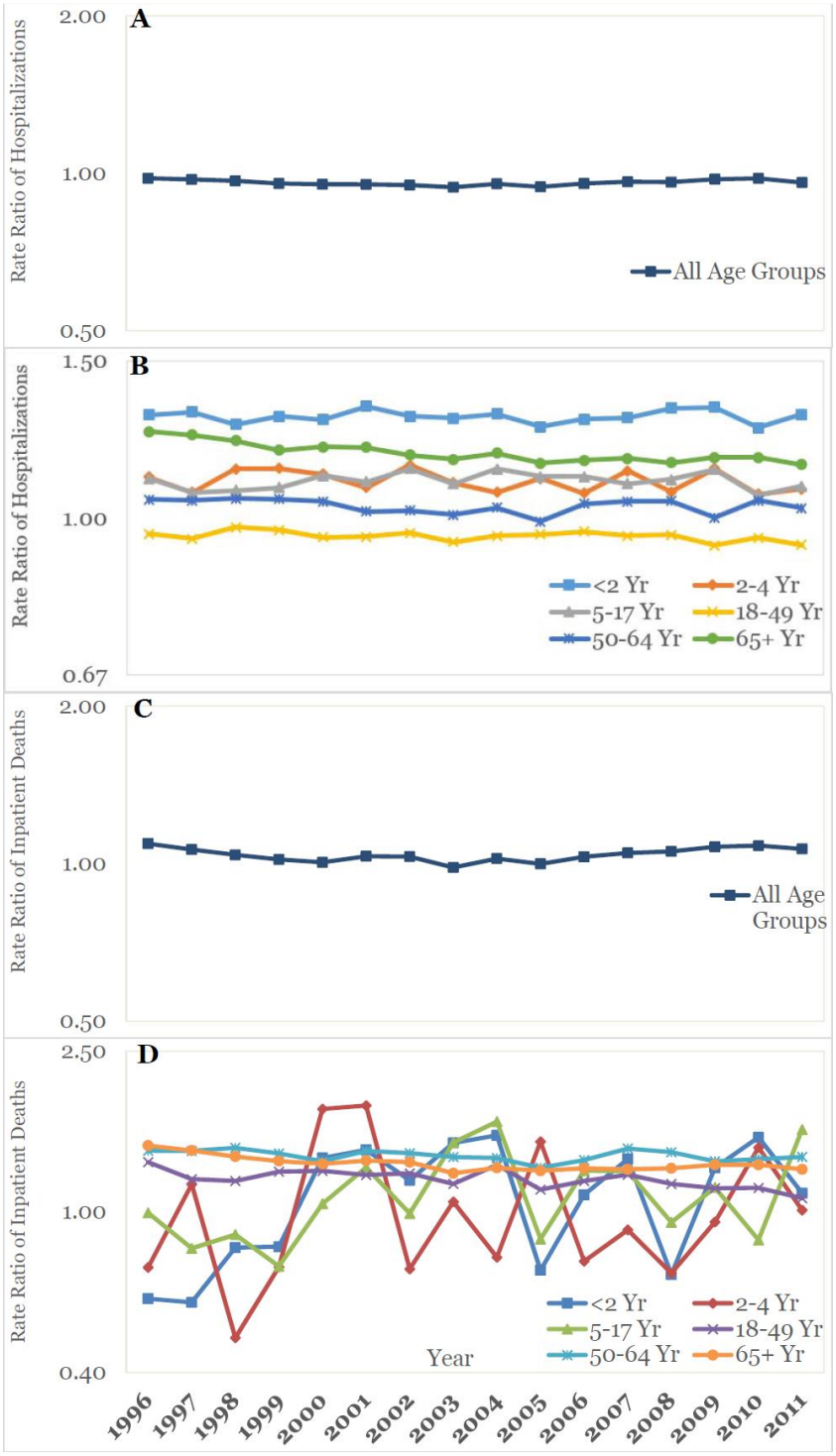

A
Rate Ratio of Hospitalizations
2.00
1.00
0.50
All Age Groups
B
Rate Ratio of Hospitalizations
1.50
1.00
0.67
<2 Yr
2-4 Yr
5-17 Yr
18-49 Yr
50-64 Yr
65+ Yr
C
Rate Ratio of Inpatient Deaths
2.00
1.00
0.50
All Age Groups
D
Rate Ratio of Inpatient Deaths
2.50
1.00
0.40
<2 Yr
2-4 Yr
5-17 Yr
18-49 Yr
50-64 Yr
65+ Yr
Year
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011

Figure S1

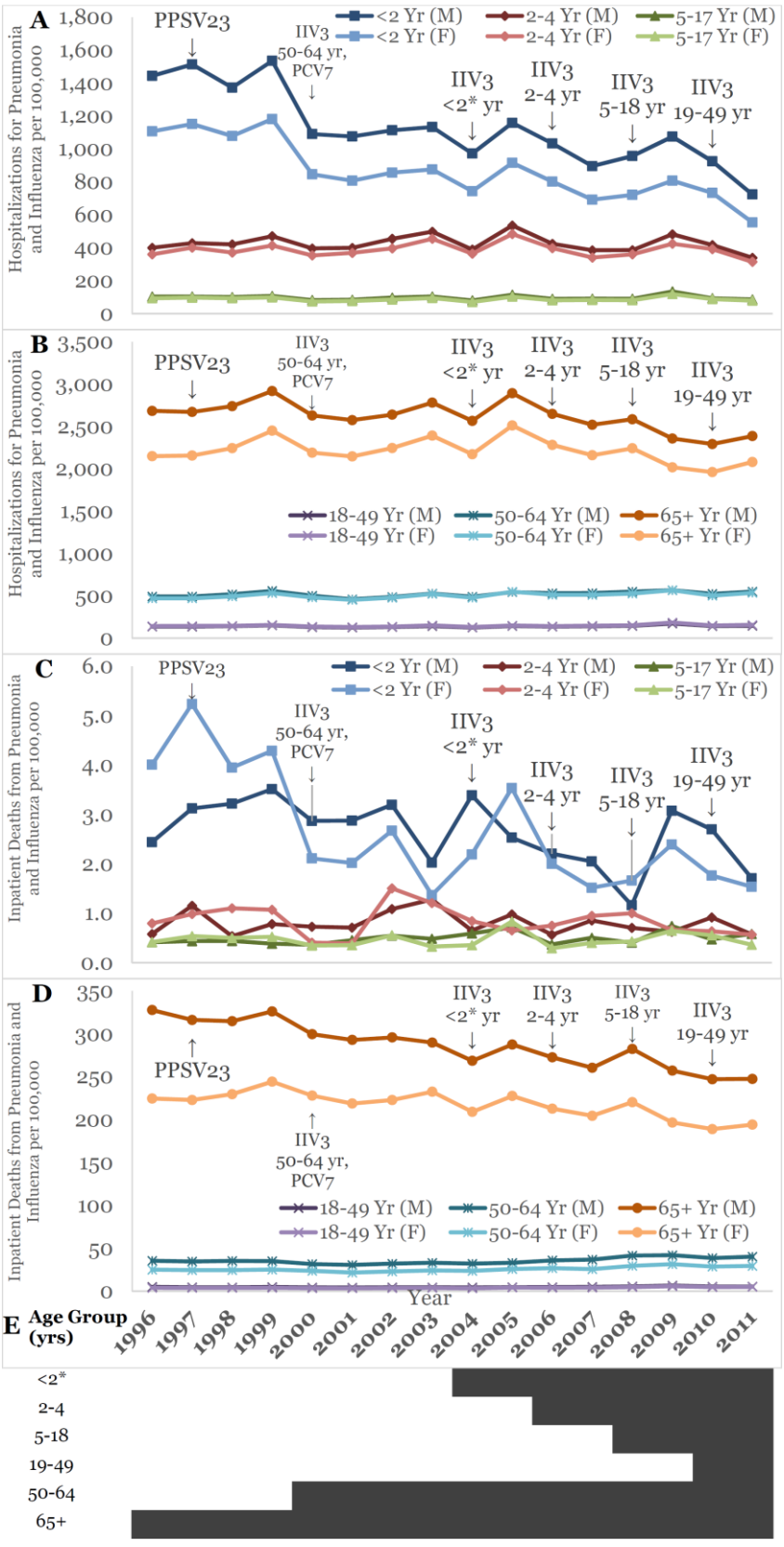
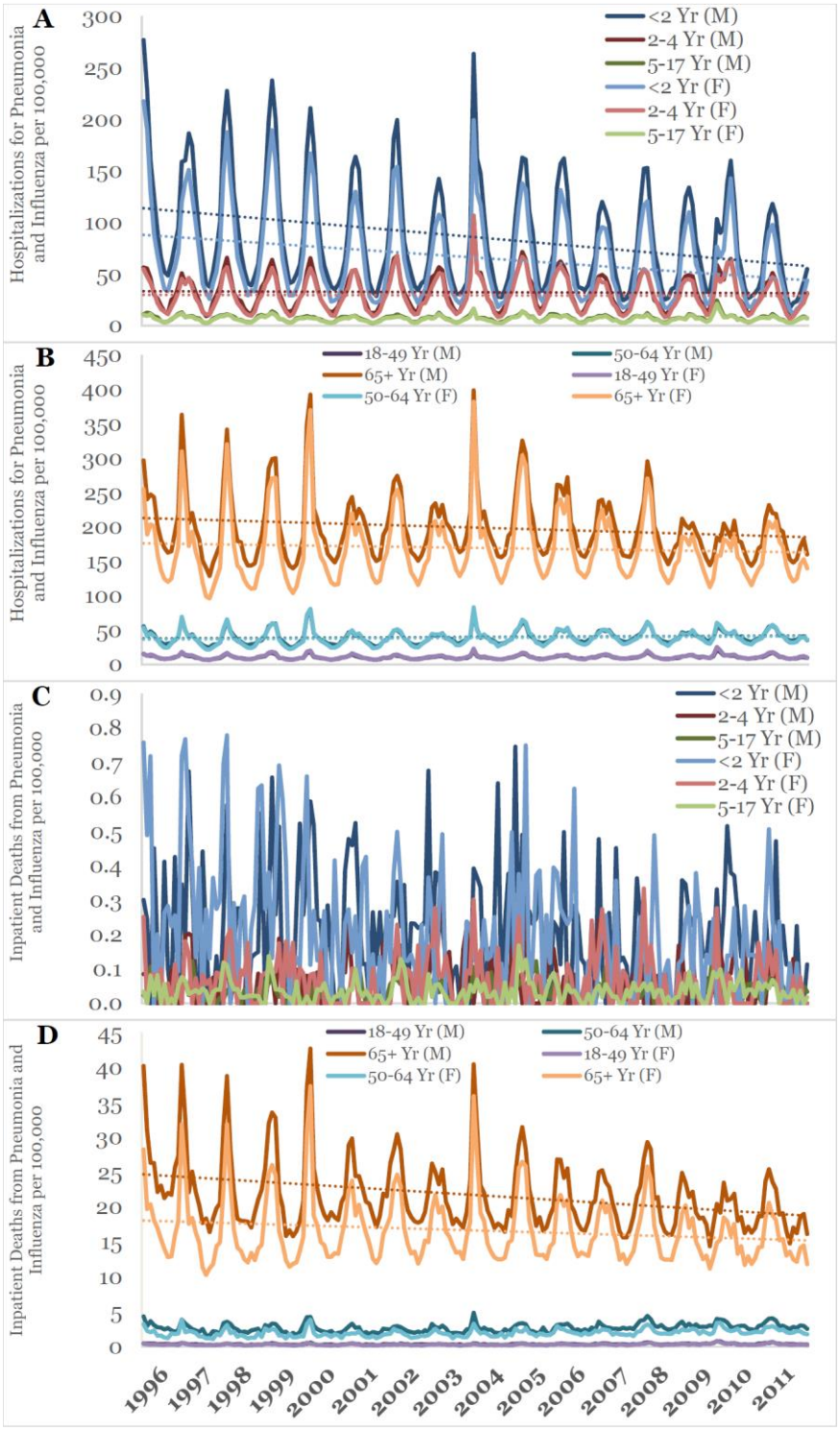

A
B
C
D
E
Hospitalizations for Pneumonia and Influenza per 100,000
Inpatient Deaths from Pneumonia and Influenza per 100,000
PPSV23
IIV3 50-64 yr, PCV7
IIV3 <2* yr
IIV3 2-4 yr
IIV3 5-18 yr
IIV3 19-49 yr
<2 Yr (M)
<2 Yr (F)
2-4 Yr (M)
2-4 Yr (F)
5-17 Yr (M)
5-17 Yr (F)
18-49 Yr (M)
18-49 Yr (F)
50-64 Yr (M)
50-64 Yr (F)
65+ Yr (M)
65+ Yr (F)
Year
Age Group (yrs)
<2*
2-4
5-18
19-49
50-64
65+

Figure S2


A
Hospitalizations for Pneumonia and Influenza per 100,000
300
250
200
150
100
50
0
<2 Yr (M)
2-4 Yr (M)
5-17 Yr (M)
<2 Yr (F)
2-4 Yr (F)
5-17 Yr (F)
B
Hospitalizations for Pneumonia and Influenza per 100,000
450
400
350
300
250
200
150
100
50
0
18-49 Yr (M)
65+ Yr (M)
50-64 Yr (F)
50-64 Yr (M)
18-49 Yr (F)
65+ Yr (F)
C
Inpatient Deaths from Pneumonia and Influenza per 100,000
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
<2 Yr (M)
2-4 Yr (M)
5-17 Yr (M)
<2 Yr (F)
2-4 Yr (F)
5-17 Yr (F)
D
Inpatient Deaths from Pneumonia and Influenza per 100,000
45
40
35
30
25
20
15
10
5
0
18-49 Yr (M)
65+ Yr (M)
50-64 Yr (F)
50-64 Yr (M)
18-49 Yr (F)
65+ Yr (F)
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011

Tables

Table 1. Sex and Age-adjusted Rate Differences, Percent Reduction, and Absolute Reduction in Hospitalizations and Inpatient Deaths from Pneumonia and Influenza in the U.S., Year 1996 vs 2011

		U.S. Population in 2011 (millions)	Difference in Rates per 100,000 n (95% CI)		Percent Reduction % (95% CI)		Absolute Reduction n (95% CI)	
Hospitalizations per 100,000								
Age Group (yrs)	**<2**	8.0	638	(500, 777)	50	(39, 61)	51,000	(40,000, 62,000)
	Male	4.1	720	(524, 917)	50	(36, 63)	29,000	(21,000, 37,000)
	Female	3.9	553	(400, 706)	50	(36, 64)	22,000	(16,000, 27,000)
	2-4	12.2	52	(-5, 109)	14	(-1, 29)	6,000	(-1,000, 13,000)
	Male	6.2	61	(-6, 128)	15	(-1, 32)	4,000	(0, 8,000)
	Female	6.0	45	(-16, 107)	13	(-5, 30)	3,000	(-1,000, 6,000)
	5-17	53.8	15	(-1, 30)	15	(-1, 31)	8,000	(0, 16,000)
	Male	27.5	18	(0, 35)	17	(0, 34)	5,000	(0, 10,000)
	Female	26.3	14	(-2, 31)	15	(-2, 33)	4,000	(-1,000, 8,000)
	18-49	135.6	-11	(-25, 2)	-8	(-18, 1)	-15,000	(-33,000, 3,000)
	Male	68.1	-9	(-23, 6)	-7	(-17, 4)	-6,000	(-16,000, 4,000)
	Female	67.5	-14	(-29, 2)	-10	(-20, 1)	-9,000	(-19,000, 1,000)
	50-64	60.6	-62	(-105, -19)	-13	(-22, -4)	-38,000	(-64,000, -11,000)
	Male	29.4	-57	(-106, -9)	-12	(-21, -2)	-17,000	(-31,000, -3,000)
	Female	31.2	-66	(-113, -20)	-14	(-24, -4)	-21,000	(-35,000, -6,000)
	65+	41.4	167	(-5, 340)	7	(0, 14)	69,000	(-2,000, 141,000)
	Male	17.9	297	(82, 512)	11	(3, 19)	53,000	(15,000, 92,000)
	Female	23.5	69	(-113, 250)	3	(-5, 12)	16,000	(-26,000, 59,000)
	Overall	311.6	26	(-11, 62)	5	(-2, 12)	81,000	(-33,000, 194,000)
	Male	153.3	44	(6, 83)	8	(1, 17)	68,000	(9,000, 127,000)
	Female	158.3	9	(-31, 48)	2	(-6, 10)	14,000	(-48,000, 77,000)

Table 1 (Continued)

Inpatient Deaths per 100,000								
Age Group (yrs)	**<2**	8.0	1.6	(0.2, 2.9)	49	(7, 92)	100	(0, 200)
	Male	4.1	0.7	(-0.9, 2.4)	30	(-37, 97)	0	(0, 100)
	Female	3.9	2.5	(0.6, 4.4)	62	(14, 109)	100	(0, 200)
	2-4	12.2	0.1	(-0.4, 0.6)	17	(-59, 92)	0	(0, 100)
	Male	6.2	0.0	(-0.7, 0.7)	1	(-115, 117)	0	(0, 0)
	Female	6.0	0.2	(-0.5, 0.9)	29	(-62, 119)	0	(0, 100)
	5-17	53.8	-0.1	(-0.3, 0.2)	-14	(-71, 42)	0	(-200, 100)
	Male	27.5	-0.2	(-0.5, 0.1)	-40	(-115, 35)	0	(-100, 0)
	Female	26.3	0.1	(-0.2, 0.3)	13	(-50, 75)	0	(-100, 100)
	18-49	135.6	-0.8	(-1.5, -0.1)	-18	(-34, -2)	-1,100	(-2,000, -100)
	Male	68.1	-0.4	(-1.3, 0.5)	-7	(-25, 11)	-200	(-900, 400)
	Female	67.5	-1.2	(-1.9, -0.4)	-32	(-52, -12)	-800	(-1,300, -300)
	50-64	60.6	-4.6	(-8.4, -0.8)	-15	(-28, -3)	-2,800	(-5,100, -500)
	Male	29.4	-4.8	(-9.8, 0.2)	-14	(-28, 1)	-1,400	(-2,900, 100)
	Female	31.2	-4.4	(-8.1, -0.7)	-18	(-33, -3)	-1,400	(-2,500, -200)
	65+	41.4	52.0	(31.1, 72.9)	19	(12, 27)	21,500	(12,900, 30,200)
	Male	17.9	80.3	(51.6, 108.9)	24	(16, 33)	14,400	(9,300, 19,500)
	Female	23.5	30.4	(9.2, 51.6)	14	(4, 23)	7,100	(2,200, 12,100)
	Overall	311.6	5.7	(2.3, 9.1)	13	(6, 23)	17,800	(7,100, 28,400)
	Male	153.3	8.3	(4.3, 12.3)	17	(10, 29)	12,700	(6,500, 18,900)
	Female	158.3	3.2	(-0.5, 6.9)	8	(-1, 18)	5,100	(-700, 10,900)

* Absolute reductions in hospitalizations and inpatient deaths were rounded to 1,000s and 100s, respectively.