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Deaths averted by influenza vaccination in the U.S. during the seasons 2005/06 through 2013/14☆

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ABSTRACT

Background*:* Excess mortality due to seasonal influenza is substantial, yet quantitative estimates of the benefit of annual vaccination programs on influenza-associated mortality are lacking.
Methods*:* We estimated the numbers of deaths averted by vaccination in four age groups (0.5 to 4, 5 to 19, 20 to 64 and ≥65 yrs.) for the nine influenza seasons from 2005/6 through 2013/14. These estimates were obtained using a Monte Carlo approach applied to weekly U.S. age group-specific estimates of influenza-associated excess mortality, monthly vaccination coverage estimates and summary seasonal influenza vaccine effectiveness estimates to obtain estimates of the number of deaths averted by vaccination. The estimates are conservative as they do not include indirect vaccination effects.
Results*:* From August, 2005 through June, 2014, we estimated that 40,127 (95% confidence interval [CI] 25,694 to 59,210) deaths were averted by influenza vaccination. We found that of all studied seasons the most deaths were averted by influenza vaccination during the 2012/13 season (9398; 95% CI 2,386 to 19,897) and the fewest during the 2009/10 pandemic (222; 95% CI 79 to 347). Of all influenza-associated deaths averted, 88.9% (95% CI 83 to 92.5%) were in people ≥65 yrs. old.
Conclusions*:* The estimated number of deaths averted by the US annual influenza vaccination program is considerable, especially among elderly adults and even when vaccine effectiveness is modest, such as in the 2012/13 season. As indirect effects ("herd immunity") of vaccination are ignored, these estimates represent lower bound estimates and are thus conservative given valid excess mortality estimates

1. Introduction

In the U.S., seasonal influenza has been estimated to be associated with an average of ~25,000 [1,2] to 35,000 [3] annual deaths. In 1960, annual influenza vaccination was recommended in the U.S. for persons aged ≥65 yrs., for those with chronic debilitating disease as well as for pregnant women [4]. Influenza vaccination recommendations were broadened over time until 2010, when annual influenza vaccination was recommended for all people ≥6 months of age [5]. Recently, Kostova et al. [6] found a substantial benefit of the current influenza vaccination program in the United States on the total number of influenza cases and hospitalizations, based on data on laboratory-confirmed influenza-associated hospitalizations. Similar estimates of mortality averted by vaccination would further help prioritize public health interventions and facilitate communications regarding the need and value of influenza prevention. We sought to estimate the number of deaths averted by annual influenza vaccination in the United States from the influenza seasons 2005/06 through 2013/14. Our aim is to provide conservative seasonal and age group-specific estimates for the number of deaths averted by the US influenza vaccination program.

2. Methods

2.1. Averted deaths formula

The number of deaths averted by influenza vaccination d_A was estimated by multiplying the number of deaths expected in the

☆ The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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Table 1
Vaccine effectiveness estimates by study type, season and age range with their respective literature references.

Season	Age range (yrs.)	Study type	VE (95% CI)	Reference
2005/06	≥0.5	TND[a]	21 (−52, 59)[b]	[10]
2005/06	18–48	RCT[c]	16 (−171, 70)	[11]
2005/06	≥5	TND	61 (26, 79)	[12]
2006/07	≥0.5	TND	52 (22, 70)	[10]
2006/07	≥9	TND	46 (17, 65)	[13]
2007/08	18–49	RCT	68 (46, 81)	[14]
2007/08	0.5–4	TND	39 (2, 62)	[15]
2007/08	≥0.5	TND	37 (22, 49)	[15]
2007/08	≥0.5	TND	60 (45, 71)	[16]
2008/09	≥0.5	TND	56 (41, 67)	[17]
2009/10	≥0.5	TND	56 (23, 75)[d]	[18]
2010/11	0.5–4	TND	67 (53, 77)	[19]
2010/11	5–19	TND	59 (45, 70)	[19]
2010/11	20–64	TND	50 (36, 62)	[19]
2010/11	≥65	TND	36 (−22, 66)	[19]
2011/12	0.5–4	TND	49 (12, 70)	[20]
2011/12	5–19	TND	50 (29, 65)	[20]
2011/12	20–64	TND	46 (28, 59)	[20]
2011/12	≥65	TND	43 (−18, 72)	[20]
2012/13	0.5–4	TND	58 (40, 71)	[21]
2012/13	5–19	TND	46 (32, 57)	[21]
2012/13	20–64	TND	52 (43, 60)	[21]
2012/13	≥65	TND	32 (0, 56)	[21]
2013/14	0.5–4	TND	47 (14, 67)	[22]
2013/14	5–19	TND	56 (37, 69)	[22]
2013/14	20–64	TND	52 (42, 61)	[22]
2013/14	≥65	TND	39 (0, 65)	[22]

[a] Case test-negative design (see, e.g.[7]).
[b] Point estimate (95% confidence interval).
[c] Randomized controlled trial.
[d] Effectiveness of monovalent pandemic vaccine.

absence of vaccination (D) by the proportion effectively vaccinated, i.e.:

$$d_A = D \times \nu\phi \quad (1)$$

where, ν denotes vaccination coverage (seasonal influenza vaccine) and ϕ denotes vaccine effectiveness (VE) of the seasonal influenza vaccine. The number of excess deaths in the absence of vaccination is calculated by dividing the number of excess deaths due to influenza under the current vaccination program (ε) by the proportion not protected by vaccination ($1 - \nu\phi$), i.e.:

$$D = \frac{\varepsilon}{1 - \nu\phi}. \quad (2)$$

Note that all quantities are indexed by time. For instance, d_A may refer to the deaths averted in a given month.

2.2. Data

2.2.1. Vaccine effectiveness (VE)

We used published estimates of VE against acute respiratory illness (ARI) due to any laboratory-confirmed influenza virus infection for the influenza seasons (Northern Hemisphere) 2005/6, through 2013/14 which were derived from either case test-negative control studies [7–9] or from randomized controlled trials, conducted in outpatient settings in North American populations. We used estimates that were from subjects of a broad age range (e.g. 6 months or older or 18–48 yrs.) or were restricted to one of our age groups (e.g. ≥65 yrs.) [10–22] (Table 1). Up to 2010/11 we mostly used the same estimates Kostova et al. [6] used for their analysis of cases and hospitalizations averted by influenza vaccination; however, we excluded one unpublished study (see reference 11 in [6]) and one study that included non-North American populations [23], added one study that had been published since [16] as well as three studies estimating VE for the three recent influenza seasons (2011/12, 2012/13 and 2013/14, respectively) [20,24,25].

Table 2
Empirical distributions of vaccine effectiveness by season and age group as they were used for the calculation of averted deaths.

Season	0.5–4 yrs	5–19 yrs	20–64 yrs	≥65 yrs
2005/06	44 (3,77)[a]	44 (3,77)	44 (3,77)	29 (2,65)
2006/07	49 (19,68)	49 (19,68)	49 (19,68)	32 (12,58)
2007/08	39 (8,62)[b]	42 (24,74)	42 (24,74)	29 (13,61)
2008/09	56 (42,67)	56 (42,67)	56 (42,67)	39 (22,59)
2009/10	56 (21,74)	56 (21,74)	56 (21,74)	36 (13,65)
2010/11	67 (52,77)[b]	59 (46,70)[b]	50 (35,61)[b]	37 (5,67)[b]
2011/12	49 (15,71)[b]	50 (30,65)[b]	45 (30,58)[b]	45 (7,74)[b]
2012/13	58 (40,70)[b]	46 (33,58)[b]	52 (43,60)[b]	31 (5,56)[b]
2013/14	47 (17,67)[b]	56 (37,69)[b]	52 (41,60)[b]	40 (7,64)[b]

[a] Point estimate in percentage (95% confidence interval).
[b] Based on age group-specific estimate.

VE is believed to decline with increasing age above ∼65 yrs. [26], but there are few published estimates of VE among those 65 yrs. old, particularly for specific seasons. If, for a particular season, no age group–specific estimates were available for persons aged ≥65 yrs. (e.g. prior to 2008/9), we assumed, in concordance with [6], the VE of that age group to be 0.7 of the VE reported for the younger age group on average (uniform distribution in the range 40%–100% to reflect uncertainty). The assumption of an average attenuation of 30% is also compatible with observations for the seasons when VE estimates for persons <65 yrs. old and ≥65 yrs. old were available (2010/11, 2011/12 and 2012/13). In those years, the average relative VE for those ≥65 yrs. old ($VE_{\geq 65}/VE_{<65}$; iteratively calculated from draws from sampling distributions) was 73% (95% CI 10% to 176%). Table 2 displays the empirical distributions of annual age group-specific VEs.

2.2.2. Vaccination coverage (VC)

Monthly VC estimates by age group were obtained from the National Health Immunization Survey (NHIS) (Dr. P Lu, CDC, personal communication). Coverage was assumed constant over a month. For the months of June and July for which no coverage estimates are available, zero coverage was assumed. To account for a two-week delay in the development of effective immunity after vaccination, we assumed that the effective coverage in a given month was the average between last month's and current month's coverage. For the season 2013/14, for which no data were available at the time of this analysis, the same monthly coverage was assumed as in 2012/13 season. Vaccination coverage increased over the study period, especially in subjects under 65 yrs. of age, but there was little change between 2011/12 and 2012/13. For example, estimated coverage, in the age group 6 months to 4 yrs., was 42.7% (95% CI 39.8%, 45.8%) and 42.6% (39.8%, 45.6%) in November, respectively, and 62.4% (58.9%, 65.9%) and 63.5% (60.0%, 67.1%), in May of the following year, respectively. The assumption of unchanged coverage thus tends to understate the number of deaths averted.

2.2.3. Mortality data

To estimate the weekly number of deaths attributable to influenza by age group we used weekly age group-specific (0.5 to 4 yrs., 5 to 19 yrs., 20 to 64 yrs., 65+ yrs.) mortality data from the National Center for Health Statistics (NCHS) for 2005 through 2012. Deaths were categorized using the International Classification of Diseases, 10th Revision (ICD-10) codes. For the purposes of estimating deaths potentially averted by the influenza vaccination program, we focused on underlying causes of death categorized as respiratory and circulatory (R&C) in nature, corresponding to ICD-10 codes I00-I99 and J00-J99. For each mortality record, a single underlying cause is listed, defined as "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury", in accordance with the rules of the International