Annals of Internal Medicine ORIGINAL RESEARCH

The Effect of Influenza Vaccination for the Elderly on Hospitalization and Mortality

An Observational Study With a Regression Discontinuity Design

Michael L. Anderson, PhD; Carlos Dobkin, PhD; and Devon Gorry, PhD

Background: Observational studies using traditional research designs suggest that influenza vaccination reduces hospitalizations and mortality among elderly persons. Accordingly, health authorities in some countries prioritize vaccination of this population. Nevertheless, questions remain about this policy's effectiveness given the potential for bias and confounding in observational data.

Objective: To determine the effectiveness of the influenza vaccine in reducing hospitalizations and mortality among elderly persons by using an observational research design that reduces the possibility of bias and confounding.

Design: A regression discontinuity design was applied to the sharp change in vaccination rate at age 65 years that resulted from an age-based vaccination policy in the United Kingdom. In this design, comparisons were limited to individuals who were near the age-65 threshold and were thus plausibly similar along most dimensions except vaccination rate.

Setting: England and Wales.

Participants: Adults aged 55 to 75 years residing in the study area during 2000 to 2014.

Intervention: Seasonal influenza vaccine.

Measurements: Hospitalization and mortality rates by month of age.

Results: The data included 170 million episodes of care and 7.6 million deaths. Turning 65 was associated with a statistically and clinically significant increase in rate of seasonal influenza vaccination. However, no evidence indicated that vaccination reduced hospitalizations or mortality among elderly persons. The estimates were precise enough to rule out results from many previous studies.

Limitation: The study relied on observational data, and its focus was limited to individuals near age 65 years.

Conclusion: Current vaccination strategies prioritizing elderly persons may be less effective than believed at reducing serious morbidity and mortality in this population, which suggests that supplementary strategies may be necessary.

Primary Funding Source: National Institute on Aging.

Ann Intern Med. doi:10.7326/M19-3075 Annals.org
For author affiliations, see end of text.
This article was published at Annals.org on 3 March 2020.

Every year, 10% to 20% of the world's population contracts influenza, with resulting societal costs of billions of dollars (1). Experts disagree about which groups to target for vaccination. Many Western European countries focus on high-risk groups, such as elderly persons and those with serious health conditions, because they bear much of the burden of influenza-related morbidity and mortality. In contrast, epidemiologic models suggest that vaccinating children—a group likely to transmit influenza—may protect high-risk groups more than vaccinating the high-risk groups themselves (2–4), and studies have shown herd effects from influenza vaccination (5–11).

The choice between the 2 strategies depends on the effectiveness of the influenza vaccine in reducing hospitalizations and mortality among elderly persons. Two clinical trials since 1970 of the standard influenza vaccine have targeted community-dwelling elderly persons (12, 13). Both showed efficacy against influenza, but neither had sufficient power to examine hospitalizations or mortality. Observational studies have found that vaccination is associated with reductions in severe illness among elderly persons, but observational studies can produce misleading results. For example, cohort and case–control studies have found 20% to 50% reductions in hospitalizations and deaths in vaccinated elderly populations (14–16), but these results may be contaminated by selection bias. Studies using another observational research design, difference-in-differences, have compared vaccinated and unvaccinated elderly persons during and outside influenza season and concluded that vaccination reduced mortality and hospitalizations (17–19). These studies found that the vaccinated populations also had lower morbidity and mortality outside influenza season, which suggests selection bias.

Our research used another observational design known as regression discontinuity. We chose this design because it has features that protect against selection bias and are not available in the other observational research designs used to study this issue.

Methods

Data Sources

We used data from patient surveys and administrative records. Vaccination data came from 2 sources.

See also:

Editorial comment

Web-Only
Supplement

The first, the Research and Surveillance Centre of the Royal College of General Practitioners, provided vaccine uptake data from 2003 to 2012 from computerized medical records at approximately 100 monitored practices of general practitioners (GPs) across England and Wales. The second source was the Primary Care Trust Patient Surveys of 2004 to 2005, which surveyed a representative sample of patients enrolled in the National Health Service across England and Wales.

Hospitalization data from 2000 to 2011 came from Hospital Episode Statistics, a data warehouse of all admissions and outpatient appointments in English National Health Service hospitals or treatment centers. Each record includes demographic information about each patient, along with International Classification of Diseases (ICD) codes identifying cause of admission (**Appendix 1**, available at Annals.org). Mortality data from 1990 to 2014 came from the Office for National Statistics. Each record includes gender, month and year of birth, month and year of death, and ICD codes that describe the underlying cause of death and sequence of conditions leading to death. Last, we obtained special tabulations from the 2001 and 2011 censuses of England and Wales to enumerate the at-risk population (**Appendix 1**).

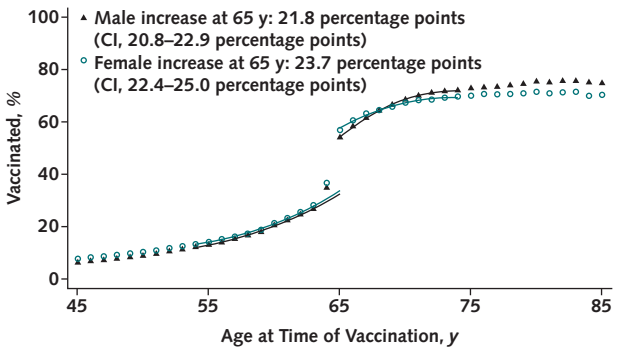
Procedures and Outcomes

We constructed 3 analytic data sets: 1 for vaccination rates, 1 for hospitalization rates, and 1 for mortality rates. We calculated all rates separately by gender.

We combined GP data with survey data to construct vaccination rates. Data from GPs reflect uptake of seasonal influenza vaccination for patients vaccinated at their GP's office. We received annual vaccination rates for 1-year age groups by gender, with data on approximately 1.06 million patients per year (9.6 million patient-years). A previous study found that the GP data are nationally representative (20). Because these data may miss vaccinations given in workplaces or pharmacies, we complemented them with patient survey data, which cover approximately 120 000 patients each year (240 000 total). Patient surveys occurred between January and April, when seasonal influenza vaccines were no longer being regularly administered, and included a 12-month retrospective question about vaccination that captured status for the previous influenza season. We constructed vaccination rates by year of age.

We calculated numerators for hospitalizations and deaths from any cause and from causes plausibly related to influenza. Our hospitalization data cover 170 million episodes of care from April 2000 to March 2011. For each hospital admission, we recorded whether an ICD code for pneumonia, influenza, respiratory diseases, or circulatory diseases appeared anywhere in the patient's list of ICD codes (**Appendix 1**). Our mortality data include 7.6 million deaths from January 2000 to December 2014. Each record includes cause of death determined by the coroner or the physician who attended the decedent's last illness. We coded death categories using the same ICD codes as used for hospitalizations.

Figure 1. Age profile of vaccination status.



Age is calculated at the time of vaccination. Vaccinations are given in September and October, so a substantial fraction of persons aged 64 y will turn 65 during the influenza season. For this reason, the regressions were fitted dropping the cell at 64 y. (Data from Royal College of General Practitioners 2003–2012.).

We identified denominators and calculated rates of hospitalization and mortality per 10 000 persons by collapsing counts to the level of month of birth by month of event (hospitalizations or mortality) and dividing by the enumerated population (in tens of thousands) in each month of birth by month of event—for example, the hospitalization rate in March 2010 for adults born in June 1943. We restricted month of event to lie between October and March, the period during which the influenza virus typically circulates in the Northern Hemisphere.

Statistical Analysis

In the 2000-to-2001 influenza season, U.K. vaccination policy was revised to prioritize vaccination of persons aged 65 years or older (**Supplement Table 1**, available at Annals.org). We used the sharp increase in vaccination rates at age 65 years (**Figure 1**) to conduct the regression discontinuity analysis (21–27). In brief, the regression discontinuity design tests whether the increase in vaccination rates was associated with a corresponding decrease in hospitalization and mortality rates. The analysis compared persons just older than versus just younger than 65 years. If these groups are similar, the analysis mimics a randomized trial for those near age 65 years. Some persons younger than 65 years were vaccinated, and some older than 65 years were not, so our study was analogous to a randomized trial with imperfect adherence (28).

We plotted age profiles of the relevant variables, visually inspected them for discontinuities, and then fitted regression models to estimate changes in vaccination rates and outcomes. Estimation proceeded in 3 steps. First, using data on persons aged 55 to 75 years, we modeled vaccination rate as a quadratic function of age using regressions estimated at the year-of-age level, with a break at age 65 years. Next, using data on persons aged 60 to 70 years, we modeled hospitalization and mortality rates as quadratic functions of age using regressions estimated at the level of month of

age by month of hospitalization or mortality, with a break at age 65 years. Finally, we divided the change in hospitalization or mortality rate when turning 65 by the change in vaccination rate when turning 65. This final step rescaled the "intention-to-treat" effect of the age-65 vaccination guideline into an actual effect of vaccination. We transformed the coefficients to percentage terms relative to the baseline rate of hospitalization at age 64 years to calculate vaccine effectiveness and associated 95% CIs (**Appendix 2**, available at Annals.org). All analyses used Stata SE, version 15.0 (StataCorp).

The range of ages to include in the regression (for example, 60 to 70 years) is a design choice that affects power. A wide age range increases power but takes the analysis further from the policy-induced discontinuity at age 65 years, potentially introducing bias. We computed the narrowest age range at which we could detect 25% effectiveness (a value lower than most cohort and case–control studies estimated) with 80% power. We found that an age range of 63.5 to 66.5 years was sufficient for all-cause hospitalizations or mortality, 59.7 to 70.3 years was sufficient for pneumonia or influenza hospitalizations, and 57.7 to 72.3 years was sufficient for pneumonia or influenza mortality.

Role of the Funding Source

Neither the National Institute on Aging nor the National Institute of Food and Agriculture had any role in the study's design, conduct, or analysis or the decision to submit the manuscript for publication.

RESULTS

At age 65 years, the rate of seasonal influenza vaccination increased 22.8 percentage points (95% CI, 21.7 to 23.9 percentage points) in the GP data and 19.3 percentage points (CI, 15.8 to 22.9 percentage points) in the survey data (**Supplement Table 2**, available at Annals.org). Changes in vaccination rate were larger for women (23.7 percentage points [CI, 22.4 to 25.0 percentage points]) than men (21.8 percentage points [CI, 20.8 to 22.9 percentage points]) in the GP data, but in the survey data men had larger changes (21.7 percentage points [CI, 17.4 to 26.1 percentage points]) than women (17.0 percentage points [CI, 14.1 to 20.0 percentage points]). The increases in vaccination rate at age 65 years were visually apparent, and the regression functions appeared sufficiently flexible to fit the age profiles (**Figure 1** and **Supplement Figure 1** [available at Annals.org]). Vaccination rates in the GP data were lower at all ages than those in the survey data, which also include vaccinations received outside physicians' offices. The pattern remained even when the sample of GP data was restricted to match the years covered by the survey data (**Supplement Figure 2**, available at Annals.org). When we estimated vaccination rate increases at age 65 years separately by season, the coefficients ranged from 18.2 to 26.2 percentage points (**Supplement Table 3**, available at Annals.org). Self-reported health, education, and gender were similar for persons just younger than and those just older than 65 years (**Supplement Table 4**, available at Annals.org).

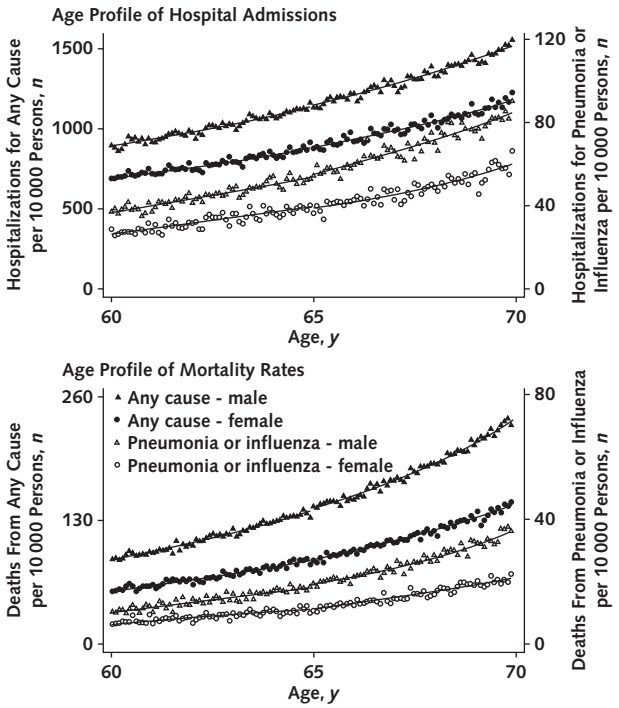
Hospitalization rates did not change significantly at age 65 years (**Table 1**). They were higher for men than women and increased with age, but the age profiles of hospitalizations for any cause and for pneumonia or influenza were smooth across the age-65 threshold for both genders (**Figure 2**, *top*). At age 65 years, total hospitalizations increased by 9.1 (CI, −1.4 to 19.6) per 10 000 persons on a base rate of 1011.8, pneumonia and influenza hospitalizations increased by 0.6 (CI, −1.5 to 2.7) per 10 000 persons on a base rate of 46.6, respiratory hospitalizations increased by 2.3 (CI, −2.8

Table 1. Hospital Admissions*

Outcome	Hospital Admissions			
	Any Cause	Pneumonia and Influenza	Respiratory	Circulatory
All				
Change in admission rate at age 65 y per 10 000 persons (95% CI)	9.1 (−1.4 to 19.6)	0.6 (−1.5 to 2.7)	2.3 (−2.8 to 7.4)	5.1 (−2.7 to 12.8)
Admission rate at age <65 y per 10 000 persons	1011.8	46.6	277.2	509.9
Effectiveness (95% CI), %	−3.9 (−8.5 to 0.6)	−5.8 (−25.3 to 12.9)	−3.6 (−11.6 to 4.3)	−4.4 (−11 to 2.3)
Men				
Change in admission rate at age 65 y per 10 000 persons (95% CI)	10.4 (−4.4 to 25.1)	1.4 (−1.4 to 4.2)	1.3 (−5.8 to 8.4)	4 (−7.0 to 15.0)
Admission rate at age <65 y per 10 000 persons	1141.8	54.0	305.7	617.4
Effectiveness (95% CI), %	−4.2 (−10.1 to 1.8)	−11.9 (−35.9 to 11.6)	−2 (−12.6 to 8.3)	−3 (−11.1 to 5.1)
Women				
Change in admission rate at age 65 y per 10 000 persons (95% CI)	7.9 (−4.1 to 19.9)	−0.1 (−2.5 to 2.2)	3.3 (−2.9 to 9.5)	6.1 (−2.3 to 14.5)
Admission rate at age <65 y per 10 000 persons	887.6	39.5	249.9	407.3
Effectiveness (95% CI), %	−3.7 (−9.4 to 1.9)	1.4 (−23.6 to 23.3)	−5.6 (−16.1 to 4.8)	−6.3 (−15 to 2.3)

* Age is computed as age on December 31 of the corresponding influenza season. All regressions include month-of-birth dummies. The regressions also include a quadratic polynomial in age fully interacted with an indicator variable for age ≥65 y. The regressions are run on 1-mo age cells weighted by the population used to compute the rate in each cell. SEs are clustered on age in months. Admissions are included in a category if there is any mention of the condition on the discharge records. The International Classification of Diseases (ICD) codes included in each category are as follows: for pneumonia and influenza, ICD, Ninth Revision (ICD-9), codes 480–488 and ICD, 10th Revision (ICD-10), codes J09–J18; for respiratory diseases, ICD-9 codes 460–519 and ICD-10 codes J00–J99; and for circulatory diseases, ICD-9 codes 390–459, 785, and 997 and ICD-10 codes I00–I99. The sample includes only admissions during the influenza season (October–March) for the 2000–2001 through 2010–2011 influenza seasons.

Figure 2. Age profile of hospital admissions (*top*) and mortality rates (*bottom*).



Influenza season is October to March, inclusive. Age is computed as age on December 31. **Top.** Includes hospitalizations during influenza seasons 2000–2001 to 2010–2011. **Bottom.** Includes deaths during influenza seasons 2000–2001 to 2013–2014.

to 7.4) per 10 000 persons on a base rate of 277.2, and circulatory hospitalizations increased by 5.1 (CI, −2.7 to 12.8) per 10 000 persons on a base rate of 509.9. When the size of the change in vaccination rate at age 65 years was taken into account, the implied effectiveness of vaccination was −3.9% (CI, −8.5% to 0.6%) for total hospitalizations, −5.8% (CI, −25.3% to 12.9%) for pneumonia and influenza hospitalizations, −3.6% (CI, −11.6% to 4.3%) for respiratory hospitalizations, and −4.4% (CI, −11.0% to 2.3%) for circulatory hospitalizations. Changes did not differ significantly between men and women for any category of hospitalization.

Mortality rates also had no significant changes for any category at age 65 years (**Table 2**). They were higher for men than women and increased with age, but the age profiles of all-cause mortality and of mortality related to pneumonia or influenza were smooth across the age-65 threshold for both genders (**Figure 2**, *bottom*). The all-cause mortality rate increased by 1.1 (CI, −1.0 to 3.3) per 10 000 persons on a base rate of 114.4, the pneumonia and influenza mortality rate increased by 0.6 (CI, −0.2 to 1.4) per 10 000 persons on a base rate of 15.0, the respiratory mortality rate increased by 0.0 (CI, −1.1 to 1.1) per 10 000 persons on a base rate of 30.3, and the circulatory mortality rate increased by 0.1 (CI, −1.1 to 1.4) per 10 000 persons on a base rate of 46.1. Rescaling these by the estimated change in vaccination rate indicates vaccine effectiveness of −4.3% (CI, −12.6% to 3.8%) for all-cause mortality, −17.3% (CI, −40.7% to 6.0%) for pneumonia and influenza deaths, −0.1% (CI, −16.2% to 14.9%) for respiratory deaths, and −1.4% (CI, −13.0% to 9.8%) for circulatory deaths. Changes did not differ significantly between men and women for any mortality category.

None of our results were sensitive to the size of the estimation window around the age-65 threshold (**Supplement Figures 3** to **7**, available at Annals.org) or to the use of linear rather than quadratic functions to model age (**Supplement Tables 5** and **6**, available at Annals.org). We found similar results when we restricted the sample period to peak influenza season, which we defined as months with rates of influenza-like illness higher than 20 cases per 10 000 persons (**Supplement Tables 7** and **8**, available at Annals.org). We did not find strong differences when stratifying the analysis by how well the vaccine matched the circulating strain of influenza (**Supplement Tables 9** and **10**, available at Annals.org), the severity of the influenza season (**Supplement Tables 11** and **12**, available at Annals.org), or the primary circulating strain of influenza (**Supplement Tables 13** and **14**, available at Annals.org).

DISCUSSION

Our results showed a sharp increase in influenza vaccination rates at age 65 years with no matching decrease in hospitalization or mortality rates.

To understand how these estimates differ from those in the existing literature, we considered whether our CIs for vaccination effects were compatible with the results of previous studies. To compare hospitalization estimates, we produced box-and-whisker plots of CIs for our hospitalization effectiveness estimates (**Figure 3**, *top*). We added estimates of average vaccine effectiveness from the literature (*bullets*) according to the following study types: cohort, case–control, and difference-in-differences. For the first 2 types, we drew on results from meta-analyses to present an overall view of the literature (14, 15). We found that typical estimates of hospitalization rates from cohort and case–control studies were outside the 95% CIs of our estimates. Difference-in-differences studies had smaller estimates, but we still rejected the hypothesis that our effects for respiratory hospitalizations were equal to the difference-in-differences estimates from a U.K.-based study (17). We did a similar comparison for mortality estimates (**Figure 3**, *bottom*). It showed that typical estimates from cohort and case–control studies differed significantly from our own, and we rejected the hypothesis that our estimates for all-cause mortality were equal to the difference-in-differences estimates from a study based in northern California (18). We concluded that our estimates of vaccination effectiveness differ from those in the literature and that the differences cannot be explained by sampling variation alone.

One explanation for these differences is that our regression discontinuity estimates were subject to less bias and confounding than the estimates from other observational studies in the literature. The direct com-

parisons between vaccinated and unvaccinated participants in cohort and case–control studies are most likely to be misleading, and these studies reported the largest effects. The difference-in-differences design can eliminate large biases, and these studies reported more modest effects (29). The regression discontinuity design that we used can eliminate even more bias, which we believe explains why our study found the smallest effects.

Alternative explanations exist. For example, we used U.K. data, and many existing studies used U.S. data. Furthermore, our study estimated effects for persons near age 65 years, whereas many existing studies estimated effects for all adults over a certain age. However, we do not believe that these explanations are plausible, because our results differ from those of other U.K.-based studies (17, 30–32) and because studies that estimated effects for different age groups typically found larger effects for persons near age 65 years than for older participants (17–19).

Another possible explanation is that the vaccinated and unvaccinated persons in our study were equally protected from infection by herd effects from vaccinations in their common contacts. However, the population we studied was roughly half vaccinated, which is below levels likely to achieve herd immunity and not markedly different from rates in previous studies.

Our study has limitations. For example, it relied on observational data, and all observational studies are at risk for producing misleading results when the intervention and control groups are not well matched. In the regression discontinuity design, the relevant factors are those that change discontinuously at the regression discontinuity threshold, which in this study was age 65 years (23). We could identify only 3 health-related factors that might change sharply at this age: frequency of health provider visits, change in employment, and vaccination with the pneumococcal vaccine.

Health provider visits may have increased at age 65 years because many persons retire at this age and have more time to attend to their health. To address this issue, we used our patient survey data to determine whether the frequency of contact with health providers changed at this age across various common types of visits and tests (**Supplement Table 15**, available at Annals.org). We found no significant changes in the frequency of contacts with health care providers at age 65 years for either gender.

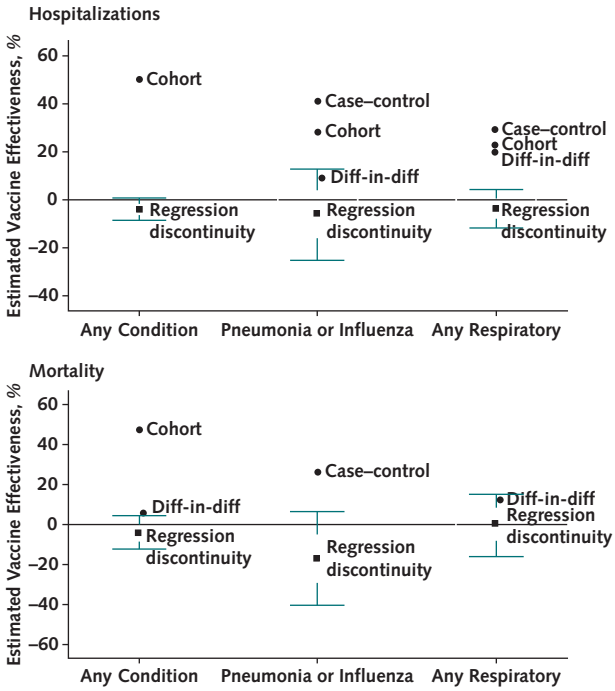
We also considered changes in employment at age 65 years using data from the Quarterly Labour Force Survey. During our sample period, men in the United Kingdom could begin receiving State Pensions at age 65 years, and for most of the period, women could begin at age 60 years. We found that at age 65 years, the male employment rate changed by −8.8 percentage points (CI, −10.7 to −6.9 percentage points) and the female employment rate by −3.1 percentage points (CI, −4.8 to −1.4 percentage points). Nevertheless, 3 facts suggest that changes in employment rate did not substantially bias our estimates in either direction. First, if retirement were affecting health, our estimates of hospitalizations and mortality should have less bias for women than men; however, we found similar effects for both genders. Second, if a negative health effect of retirement were offsetting a positive health effect of vaccination, hospitalization and mortality rates outside influenza season should have increased at age 65 years. We found no such effect for any type of hospitalization

Table 2. Mortality*

Outcome	Mortality			
	Any Cause	Pneumonia and Influenza	Respiratory	Circulatory
All				
Change in mortality rate at age 65 y per 10 000 persons (95% CI)	1.1 (−1.0 to 3.3)	0.6 (−0.2 to 1.4)	0 (−1.1 to 1.1)	0.1 (−1.1 to 1.4)
Mortality rate at age <65 y per 10 000 persons	114.4	15.0	30.3	46.1
Effectiveness (95% CI), %	−4.3 (−12.6 to 3.8)	−17.3 (−40.7 to 6)	−0.1 (−16.2 to 14.9)	−1.4 (−13 to 9.8)
Men				
Change in mortality rate at age 65 y per 10 000 persons (95% CI)	2.7 (−0.5 to 6.0)	1.1 (−0.1 to 2.3)	0.6 (−1.1 to 2.3)	0.6 (−1.5 to 2.7)
Mortality rate at age <65 y per 10 000 persons	140.6	18.7	37.5	63.3
Effectiveness (95% CI), %	−8.9 (−19.6 to 1.8)	−26.5 (−56.1 to 3)	−7.2 (−28.2 to 13)	−4.2 (−19.4 to 10.4)
Women				
Change in mortality rate at age 65 y per 10 000 persons (95% CI)	−0.4 (−2.9 to 2.2)	0.1 (−0.8 to 1.1)	−0.5 (−1.8 to 0.8)	−0.3 (−1.6 to 1.1)
Mortality rate at age <65 y per 10 000 persons	89.3	11.5	23.4	29.7
Effectiveness (95% CI), %	1.7 (−10.2 to 12.7)	−4.7 (−39.2 to 25.8)	9.1 (−14.1 to 28.3)	3.5 (−15.7 to 20.4)

* Age is computed as age on December 31 of the corresponding influenza season. All regressions include month-of-birth dummies. The regressions also include a quadratic polynomial in age fully interacted with an indicator variable for age ≥65 y. The regressions are run on 1-mo age cells weighted by the population used to compute the rate in each cell. SEs are clustered on age in months. Deaths are included in a category if there is any mention of the condition on the death certificates. The International Classification of Diseases (ICD) codes included in each category are as follows: for pneumonia and influenza, ICD, Ninth Revision (ICD-9), codes 480–488 and ICD, 10th Revision (ICD-10), codes J09–J18; for respiratory diseases, ICD-9 codes 460–519 and ICD-10 codes J00–J99; and for circulatory diseases, ICD-9 codes 390–459, 785, and 997 and ICD-10 codes I00–I99. The sample includes only deaths during the influenza season (October–March) for the 2000–2001 through 2013–2014 influenza seasons.

Figure 3. Comparing regression discontinuity estimates with estimates from existing literature for hospitalizations (*top*) and mortality (*bottom*).



The bullets denote the average estimates of difference-in-differences, cohort, and case–control studies from the literature. For our regression discontinuity study, squares denote our best estimate of vaccine effectiveness and whiskers (*horizontal green lines*) denote the 95% CIs for those estimates. Diff-in-diff = difference-in-differences.

or cause of death (**Supplement Tables 16** and **17**, available at Annals.org). Third, the age-65 vaccination guidelines were instituted in the 2000-to-2001 influenza season, so before the end of 2000 any effect of retirement was uncontaminated by changes in vaccination rate. As a result, we should have been able to identify an isolated retirement effect from 1992 to 2000, but we found no statistically significant effect of retirement on all-cause mortality or mortality from pneumonia and influenza for men turning 65 during this period (**Supplement Table 18**, available at Annals.org).

Vaccination against pneumococcal infection at age 65 years was also recommended during our study period. Pneumococcal vaccination could interact with a positive effect from influenza vaccination to produce our results only if the vaccines interfered with each other or if the former produced a negative effect that counteracted the latter's positive effect. We believe that these possibilities are unlikely.

The other limitation of our study was the focus on persons near age 65 years who responded to the vaccination guidelines. For several reasons, we believe that our estimates captured a large share of the benefits of vaccinating adults older than 65 years. First, persons in our regression discontinuity sample (aged 60 to 70 years) accounted for 23% of influenza hospitalizations and about 20% of influenza deaths occurring between ages 45 and 90 years. The mortality shares become larger when weighted by expected life-years remaining because the median decedent or inpatient in this group was older than 65 years. Second, immune response declines with age (33–35), so vaccine effectiveness was likely to be lower for 80- to 90-year-olds than for 60- to 70-year-olds. In that sense, our small estimates probably represent an upper bound on the average effectiveness of the vaccine for persons older than 65 years.

A minority of persons younger than 65 years received the vaccine. They had poorer average health than those who began vaccination at age 65 years (**Supplement Table 19**, available at Annals.org), and some likely were immunocompromised or had medical conditions. Our results cannot speak directly to the vaccine's effectiveness in this population. However, because the vaccine is less effective in immunocompromised persons (36–39), we expect that our estimates represent an upper bound on its effectiveness in the near-elderly immunocompromised population.

Evidence from a few randomized controlled trials has suggested that the influenza vaccine confers some protection against influenza-like illness in elderly persons. Our findings suggest that its effects on hospitalizations and mortality are modest at best. Two factors could explain how the vaccine might reduce influenza but not more serious outcomes. First, only a minority of hospitalizations or deaths may be attributable to influenza. A recent study estimated that only 2% to 10% of pneumococcal cases over an entire year are caused by influenza (40). Even if the influenza vaccine achieved 50% effectiveness among elderly persons, the net reduction in pneumococcal cases would be only 1% to 5%, which lies within the CIs of our estimates for this outcome. Nevertheless, during peak influenza season, the fraction of pneumococcal cases caused by influenza may reach 40% (40), and our analysis focused on the October-to-March period.

A second factor that may help explain our results is immune-response heterogeneity. The influenza vaccine is less effective in immunocompromised persons, who also face the highest risk for serious influenza-related complications. Thus, even if the influenza vaccine were effective at reducing influenza-like illness for the typical elderly recipient, it would be less effective among elderly persons at high risk for hospitalization or death. Heterogeneity in immune response among elderly persons could therefore reconcile effectiveness against influenza-like illness with less effectiveness against more serious outcomes.

In conclusion, our results do not preclude modest effectiveness of the influenza vaccine against severe outcomes in elderly persons. Therefore, continued vaccination of this population, particularly with high-dose vaccines, seems appropriate. Our findings raise questions, however, about the overall effectiveness of a vaccination strategy that is limited to standard vaccines and focuses too much on elderly persons. Supplementary strategies, such as vaccinating children and others

who are most likely to spread influenza, may also be necessary to address the high burden of influenza-related complications among older adults (41).

From University of California, Berkeley, Berkeley, California, and National Bureau of Economic Research, Cambridge, Massachusetts (M.L.A.); University of California, Santa Cruz, Santa Cruz, California, and National Bureau of Economic Research, Cambridge, Massachusetts (C.D.); and Clemson University, Clemson, South Carolina (D.G.).

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the U.S. Department of Agriculture.

Acknowledgment: The authors thank seminar participants at ASHEcon; Brigham Young University; Clemson University; University of California, Irvine; University of Connecticut; University of Illinois at Urbana-Champaign; and University of South Carolina.

Grant Support: By award R01AG044796 from the National Institute on Aging of the National Institutes of Health and by Hatch project 233535 from the National Institute of Food and Agriculture of the U.S. Department of Agriculture. Eighty percent of the project was funded by federal sources, and none was funded by nongovernmental sources.

Disclosures: Drs. Anderson, Dobkin, and Gorry report grants from the National Institute on Aging of the National Institutes of Health during the conduct of the study. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-3075.

Reproducible Research Statement: *Study protocol:* Not available. *Statistical code:* Available at https://doi.org/10.6078/D1Q11H. *Data set:* Available for purchase from the Royal College of General Practitioners Research and Surveillance Centre, the U.K. Office for National Statistics, the U.K. National Health Service Hospital Episode Statistics, the U.K. Data Archive, and Picker Institute Europe. The code archive provides details.

Corresponding Author: Michael L. Anderson, PhD, 714 University Hall, MC3310, University of California, Berkeley, Berkeley, CA 94720; e-mail, mlanderson@berkeley.edu.

Current author addresses and author contributions are available at Annals.org.

References

1. **Peasah SK, Azziz-Baumgartner E, Breese J, et al.** Influenza cost and cost-effectiveness studies globally—a review. Vaccine. 2013;31:5339-48. [PMID: 24055351] doi:10.1016/j.vaccine.2013.09.013
2. **Longini IM Jr, Halloran ME.** Strategy for distribution of influenza vaccine to high-risk groups and children. Am J Epidemiol. 2005;161:303-6. [PMID: 15692073]
3. **Basta NE, Chao DL, Halloran ME, et al.** Strategies for pandemic and seasonal influenza vaccination of schoolchildren in the United States. Am J Epidemiol. 2009;170:679-86. [PMID: 19679750] doi:10.1093/aje/kwp237
4. **Medlock J, Galvani AP.** Optimizing influenza vaccine distribution. Science. 2009;325:1705-8. [PMID: 19696313] doi:10.1126/science.1175570
5. **Monto AS, Davenport FM, Napier JA, et al.** Modification of an outbreak of influenza in Tecumseh, Michigan by vaccination of schoolchildren. J Infect Dis. 1970;122:16-25. [PMID: 5433709]
6. **Rudenko LG, Slepushkin AN, Monto AS, et al.** Efficacy of live attenuated and inactivated influenza vaccines in schoolchildren and their unvaccinated contacts in Novgorod, Russia. J Infect Dis. 1993;168:881-7. [PMID: 8376833]
7. **Hurwitz ES, Haber M, Chang A, et al.** Effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts. JAMA. 2000;284:1677-82. [PMID: 11015798]
8. **Ghendon YZ, Kaira AN, Elshina GA.** The effect of mass influenza immunization in children on the morbidity of the unvaccinated elderly. Epidemiol Infect. 2006;134:71-8. [PMID: 16316494]
9. **Glezen WP.** Herd protection against influenza. J Clin Virol. 2006;37:237-43. [PMID: 17008123]
10. **King JC Jr, Stoddard JJ, Gaglani MJ, et al.** Effectiveness of school-based influenza vaccination. N Engl J Med. 2006;355:2523-32. [PMID: 17167135]
11. **Loeb M, Russell ML, Moss L, et al.** Effect of influenza vaccination of children on infection rates in Hutterite communities: a randomized trial. JAMA. 2010;303:943-50. [PMID: 20215608] doi:10.1001/jama.2010.250
12. **Govaert TM, Thijs CT, Masurel N, et al.** The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. JAMA. 1994;272:1661-5. [PMID: 7966893]
13. **Allsup S, Haycox A, Regan M, et al.** Is influenza vaccination cost effective for healthy people between ages 65 and 74 years? A randomised controlled trial. Vaccine. 2004;23:639-45. [PMID: 15542184]
14. **Gross PA, Hermogenes AW, Sacks HS, et al.** The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. Ann Intern Med. 1995;123:518-27. [PMID: 7661497]
15. **Jefferson T, Rivetti D, Rivetti A, et al.** Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. Lancet. 2005;366:1165-74. [PMID: 16198765]
16. **Nichol KL, Nordin JD, Nelson DB, et al.** Effectiveness of influenza vaccine in the community-dwelling elderly. N Engl J Med. 2007;357:1373-81. [PMID: 17914038]
17. **Mangtani P, Cumberland P, Hodgson CR, et al.** A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom General Practice Research Database. J Infect Dis. 2004;190:1-10. [PMID: 15195237]
18. **Fireman B, Lee J, Lewis N, et al.** Influenza vaccination and mortality: differentiating vaccine effects from bias. Am J Epidemiol. 2009;170:650-6. [PMID: 19625341] doi:10.1093/aje/kwp173
19. **Baxter R, Ray GT, Fireman BH.** Effect of influenza vaccination on hospitalizations in persons aged 50 years and older. Vaccine. 2010;28:7267-72. [PMID: 20832494] doi:10.1016/j.vaccine.2010.08.088
20. **Correa A, Hinton W, McGovern A, et al.** Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) sentinel network: a cohort profile. BMJ Open. 2016;6:e011092. [PMID: 27098827] doi:10.1136/bmjopen-2016-011092
21. **Bor J, Moscoe E, Mutevedzi P, et al.** Regression discontinuity designs in epidemiology: causal inference without randomized trials. Epidemiology. 2014;25:729-37. [PMID: 25061922] doi:10.1097/EDE.0000000000000138
22. **O'Keeffe AG, Geneletti S, Baio G, et al.** Regression discontinuity designs: an approach to the evaluation of treatment efficacy in primary care using observational data. BMJ. 2014;349:g5293. [PMID: 25199521] doi:10.1136/bmj.g5293
23. **Venkataramani AS, Bor J, Jena AB.** Regression discontinuity designs in healthcare research. BMJ. 2016;352:i1216. [PMID: 26977086] doi:10.1136/bmj.i1216
24. **Sood N, Bendavid E, Mukherji A, et al.** Government health insurance for people below poverty line in India: quasi-experimental eval-

uation of insurance and health outcomes. BMJ. 2014;349:g5114. [PMID: 25214509] doi:10.1136/bmj.g5114
25. **Stevenson AJ, Flores-Vazquez IM, Allgeyer RL, et al.** Effect of removal of Planned Parenthood from the Texas Women's Health Program. N Engl J Med. 2016;374:853-60. [PMID: 26836435] doi:10.1056/NEJMsa1511902
26. **Chen H, Li Q, Kaufman JS, et al.** Effect of air quality alerts on human health: a regression discontinuity analysis in Toronto, Canada. Lancet Planet Health. 2018;2:e19-26. [PMID: 29615204] doi:10.1016/S2542-5196(17)30185-7
27. **Melamed A, Fink G, Wright AA, et al.** Effect of adoption of neoadjuvant chemotherapy for advanced ovarian cancer on all cause mortality: quasi-experimental study. BMJ. 2018;360:j5463. [PMID: 29298771] doi:10.1136/bmj.j5463
28. **Imbens GW, Lemieux T.** Regression discontinuity designs: a guide to practice. J Econom. 2008;142:615-35. doi:10.1016/j.jeconom.2007.05.001
29. **Dimick JB, Ryan AM.** Methods for evaluating changes in health care policy: the difference-in-differences approach. JAMA. 2014;312:2401-2. [PMID: 25490331] doi:10.1001/jama.2014.16153
30. **Ahmed AE, Nicholson KG, Nguyen-Van-Tam JS.** Reduction in mortality associated with influenza vaccine during 1989-90 epidemic. Lancet. 1995;346:591-5. [PMID: 7651002]
31. **Fleming DM, Watson JM, Nicholas S, et al.** Study of the effectiveness of influenza vaccination in the elderly in the epidemic of 1989-90 using a general practice database. Epidemiol Infect. 1995;115:581-9. [PMID: 8557090]
32. **Ahmed AH, Nicholson KG, Nguyen-van Tam JS, et al.** Effectiveness of influenza vaccine in reducing hospital admissions during the 1989-90 epidemic. Epidemiol Infect. 1997;118:27-33. [PMID: 9042032]
33. **Miller RA.** Aging and immune function. Int Rev Cytol. 1991;124:187-215. [PMID: 2001916]
34. **Miller RA.** The aging immune system: primer and prospectus. Science. 1996;273:70-4. [PMID: 8658199]
35. **Yung RL.** Changes in immune function with age. Rheum Dis Clin North Am. 2000;26:455-73. [PMID: 10989507]
36. **Kumar SS, Ventura AK, VanderWerf B.** Influenza vaccination in renal transplant recipients. JAMA. 1978;239:840-2. [PMID: 342736]
37. **Gross PA, Lee H, Wolff JA, et al.** Influenza immunization in immunosuppressed children. J Pediatr. 1978;92:30-5. [PMID: 619076]
38. **Kiecolt-Glaser JK, Glaser R, Gravenstein S, et al.** Chronic stress alters the immune response to influenza virus vaccine in older adults. Proc Natl Acad Sci U S A. 1996;93:3043-7. [PMID: 8610165]
39. **Tasker SA, Treanor JJ, Paxton WB, et al.** Efficacy of influenza vaccination in HIV-infected persons. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1999;131:430-3. [PMID: 10498559]
40. **Shrestha S, Foxman B, Weinberger DM, et al.** Identifying the interaction between influenza and pneumococcal pneumonia using incidence data. Sci Transl Med. 2013;5:191ra84. [PMID: 23803706] doi:10.1126/scitranslmed.3005982
41. **Ward CJ.** Influenza vaccination campaigns: is an ounce of prevention worth a pound of cure? Am Econ J Appl Econ. 2014;6:38-72. doi:10.1257/app.6.1.38

Current Author Addresses: Dr. Anderson: 714 University Hall, MC3310, University of California, Berkeley, Berkeley, CA 94720.
Dr. Dobkin: 441 Engineering 2, University of California, Santa Cruz, 1156 High Street, Santa Cruz, CA 95064.
Dr. Gorry: John E. Walker Department of Economics, 228 Sirrine Hall, Clemson, SC 29634.

Author Contributions: Conception and design: M.L. Anderson, C. Dobkin, D. Gorry.
Analysis and interpretation of the data: M.L. Anderson, C. Dobkin, D. Gorry.
Drafting of the article: M.L. Anderson, C. Dobkin, D. Gorry.
Critical revision of the article for important intellectual content: M.L. Anderson, C. Dobkin, D. Gorry.
Final approval of the article: M.L. Anderson, C. Dobkin, D. Gorry.
Provision of study materials or patients: C. Dobkin.
Statistical expertise: M.L. Anderson, C. Dobkin, D. Gorry.
Obtaining of funding: M.L. Anderson, C. Dobkin, D. Gorry.
Administrative, technical, or logistic support: C. Dobkin.
Collection and assembly of data: C. Dobkin, D. Gorry.

Appendix 1: Data Appendix

Hospital Episode Statistics Inpatient Data

These data sets capture episodes of admitted patient care delivered at National Health Service hospitals in England or care commissioned by the National Health Service in other settings. Each record includes month of birth, gender, date of admission to the hospital, a detailed description of the treatment received during the hospital stay, and up to 20 ICD codes describing the patient's medical conditions. We focused on file years 2000 to 2010, which include episodes ending between April 2000 and March 2011.

Each file year has between 12 million and 19 million episodes of care, for a total of 169 900 052 episodes for file years 2000 to 2010, inclusive. We first dropped episodes coded as not completed within the file year because these are duplicate records and the information contained in them appears in the following file year. This resulted in dropping 778 130 episodes and left 169 121 922 episodes. Each element of the Hospital Episode Statistics inpatient data corresponds to a single inpatient episode. Most hospitalizations are captured in a single episode, but about 22% of episodes are part of a sequential chain of episodes that make up a single hospitalization and capture the treatment provided as a person is moved within or across hospitals. We used date of admission and date of discharge, along with a patient identifier, to aggregate across the episodes that make up each hospitalization. A small proportion of episodes (39 602 of 169 121 922) are missing one of the variables needed to link them to other episodes; we treated each of these as a complete hospitalization despite a chance that they were part of a multiepisode hospital stay. Combining the information from sequential episodes into a single hospitalization record resulted in a data set with 146 327 850 records, where each record corresponds to a completed hospital admission.

The definition of hospital admission in these data is broader than that used in the United States. The Hospital Episode Statistics inpatient data include 5 types of admissions: ordinary admissions, day-case admissions, regular day admissions, regular night admissions, and mothers and babies using only delivery facilities. Ordinary admissions include nonelective admissions and elective admissions for which an overnight stay in the hospital is anticipated. Also included in this category are persons scheduled for a treatment during the day who end up staying overnight. Day-case admissions are persons admitted electively who receive treatment during the day and do not stay overnight. These are largely for such procedures as endoscopies and cataract removals. Regular day admissions are persons admitted for treatment during the day as part of a planned series of treatments for an ongoing condition. They are largely coming in for hemodialysis, chemotherapy, or radiation treatment. Regular night admissions are similar to regular day admissions except the treatment is done overnight; these hospitalizations are rare. The first and fifth categories are what we would observe in a typical inpatient data set in the United States, whereas the other treatments would end up in an ambulatory procedure data set.

For each hospitalization, we coded up indicator variables both for the primary cause of admission and for any evidence of a particular condition. For example, we created an indicator variable for influenza or pneumonia that takes on a value of 1 if influenza or pneumonia is the primary cause of admission. We also created an indicator variable that takes on a value of 1 if an ICD code for pneumonia or influenza is anywhere in the 20 ICD codes of any of the spells that compose a hospitalization. The ICD codes included in each admission category are as follows: for influenza, ICD, Ninth Revision (ICD-9), codes 487 to 488 and ICD, 10th Revision (ICD-10), codes J09 to J11; for pneumonia and influenza, ICD-9 codes 480 to 488 and ICD-10 codes J09 to J18; for respiratory diseases, ICD-9 codes 460 to 519 and ICD-10 codes J00 to J99; and for circulatory diseases, ICD-9 codes 390 to 459, 785, and 997 and ICD-10 codes I00 to I99.

The **Appendix Table** presents the number of all types of admissions, ordinary admissions, and emergency admissions for each cause. Comparing across rows as we restrict the sample first to ordinary admissions and then to emergency admissions (which are a subset of ordinary admissions) shows that for the principal outcome we focus on in the analysis, pneumonia and influenza, the restrictions result in dropping very few cases despite reducing the total sample size substantially. The inclusion of elective admissions or

planned treatments would primarily increase the amount of noise in the data. For this reason, we focused on emergency admissions in our analysis. However, estimates from the sample of all hospital admissions and ordinary admissions give very similar results.

Creation of Population Denominators for Rates

To create hospitalization and death rates by month for each month-of-birth cohort, we created a population file with estimates of the number of persons who were alive in a particular month for each cohort. An example observation is the number of men born in February 1943 who were alive in April 2007. To create these population estimates for England and Wales, we used mortality records and month-level tabulations prepared for us from the 2001 and 2011 censuses. To estimate the population between censuses, we followed the methodology of the U.S. Census Bureau. Population levels for persons born in month m were given by the following difference equation:

$$(1)\ Q_{m,t} = Q_{m,t-1} + Births_{m,t} - Deaths_{m,t} + Migration_{m,t}$$

where t is the months elapsed since the 2001 census and $Q_{m,t}$ is the population estimate for cohort m at the end of month t. The other 3 variables are births, deaths, and net migration into England and Wales for cohort m in month t. We do not have cohort-specific birth counts or net migration. The lack of birth counts was not relevant because we were generating population estimates only for adults, but the lack of cohort-specific net migration was a problem for younger populations. **Appendix Figure 1**, however, suggests that migration rates for our population of interest, 60- to 70-year-olds, were low. Because of the data limitations, rather than use **Equation 1**, we estimated intercensal populations using the following equation:

$$(2)\ Q_{m,t} = Q_{m,t-1} - Deaths_{m,t}$$

We set the first period estimate, $Q_{m,0}$, equal to the population in the 2001 census, which was conducted at the end of April. We then subtracted the deaths of persons in cohort m that occurred in each of the following 119 months until we reached March 2011, which was when the 2011 census occurred. To determine how well we captured the changes in population size, we compared our estimates of the population in March 2011 based on **Equation 2** with the actual March 2011 census counts.

Appendix Figure 1 shows the percentage difference between the population in the 2011 census and our estimate based on **Equation 2**. The figure reveals that net migration affects our estimates for younger cohorts but that the cohorts we are interested in, persons aged 60 to 70 years, had low migration rates. The estimates for older cohorts are imprecise because of small sample sizes. The estimates for elderly persons are also systematically too high, which may be the result of the probability of responding to the census declining with age. In addition, slippage was very large for persons around 92 years old. A careful examination of the underlying age profiles suggests that this is due to an overcount in the 2001 census of persons born between January and December 1919. This may have occurred from a small fraction of persons born in 1991 transposing the last 2 digits of their birth year when entering it on the census form. Fortunately, this issue is outside the age range we examine, and the average amount of slippage for the cohorts of interest is only about 1%.

We adjusted for the slippage in our estimates using the same approach as used by the U.S. Census Bureau to estimate intercensal populations (42). We started with $Q_{m,0}$, $Q_{m,1}$, . . . , $Q_{m,119}$, as estimated from **Equation 2**, and then adjusted for the gap between our predicted population in March 2011 based on the 2001 census ($Q_{m,119}$) and the actual 2011 census population using the following equation:

$$(3)\ P_{m,t} = Q_{m,t}\left(Census\ 2011_m / Q_{m,119}\right)^{t/119}$$

where $P_{m,t}$ denotes our population estimate for cohort m in month t and $Census\ 2011_m$ denotes the census estimate of cohort m from the 2011 census. As noted earlier, we set $Q_{m,0}$ equal to the population estimate from the 2001 census. As can be seen from **Equation 3**, when $t = 119$ the population estimate is equal to the 2011 census. In the intervening 118 months, the gap between the population estimate based on **Equation 2** and the actual 2011 census was incrementally adjusted for.

Because we have mortality data up until 2014, we continued population estimates through 2014. The next census is in 2021, so we used **Equation 2** to estimate population counts and could not adjust for the slippage due to migration. As noted earlier, even over a 10-year period our cohorts of interest had relatively little net migration, so this is unlikely to be a meaningful issue for the 3-year period from 2011 to 2014. We took a similar approach to get estimates for the 1 year before the 2001 census for which we needed population denominators. Because our hospital data have records for England but not Wales, we also needed England-specific population estimates. We could not get mortality data for England alone that would allow us to create estimates using the described approach because of concerns about shadow disclosure. For this reason, we estimated the population in England by multiplying the estimates from **Equation 3** by the fraction of each cohort from the 2001 census of England and Wales that resided in England. This is a modest adjustment because only about 5% of the population resided in Wales. **Appendix Figure 2** plots population and hospitalization data for England by age. The black dots in the figure show the well-known variation in population size across birth months. Unsurprisingly, hospitalization counts, which are presented in blue, demonstrate the

same pattern. The red dots are hospitalization rates, and they show that using the cohort-specific population estimates described earlier to estimate hospitalization rates substantially reduces the monthly variability of the rates.

Appendix 2: Technical Appendix

Regression Discontinuity Design

Because age was not the sole determinant of vaccination status, we implemented a 2-stage "fuzzy" regression discontinuity design. This design is analogous to a randomized experiment with imperfect adherence. A benefit of the regression discontinuity design is transparency: We plotted age profiles of the relevant variables to visually inspect for discontinuities and then fitted regression models to estimate changes in treatments or outcomes.

To determine if the policy affected vaccination, we tested for a discontinuous change in vaccination rates at age 65 years. We specified vaccination rates as a function of age using local polynomial regressions estimated at the year-of-age level. In these "first-stage" regressions, the coefficient of interest was an indicator variable signifying age 65 years and older, and we controlled for a quadratic in age and an interaction between that quadratic and the indicator for age 65 years and older. We limited the sample to a bandwidth of 10 years of age around the age-65 threshold in our baseline regression (that is, persons aged 55 to 75 years) and checked robustness to using alternative bandwidths (**Supplement Figures 3** to **7**). Our regressions weighted each year-of-age observation by the number of patients or survey respondents of that age. We computed robust SEs to generate 95% CIs. The first-stage regressions took the form:

$$V_a = \theta_0 + \theta_1 Z_a + \theta_2 \tilde{A}_a + \theta_3 \tilde{A}_a Z_a + \theta_4 \tilde{A}_a^2 + \theta_5 \tilde{A}_a^2 Z_a + u_a$$

The dependent variable was the vaccination rate for individuals of age a. Z_a was an indicator equal to unity if $a \geq 65$ years and 0 otherwise. $\tilde{A}_a$ was the running variable, or age in years, normalized such that $\tilde{A}_a = 0$ when $a = 65$ years of age. The coefficient of interest, θ_1, represents the first-stage effect of the vaccination policy on the vaccination rate V_a. Our regressions weighted each observation by the number of patients or survey respondents of age a.

To determine if the sharp, policy-induced increase in vaccination rates at age 65 years affected hospitalizations or mortality, we tested for discontinuous changes in these outcomes at age 65 years. We specified hospitalization and mortality rates as functions of age using local polynomial regressions estimated at the month-of-age by month-of-event level. The coefficient of interest was again an indicator variable signifying age 65 years and older, and we controlled for a quadratic in age and an interaction between that quadratic and the indicator for age 65 years and older. For additional precision, we included month-of-birth indicators. We limited the sample to a bandwidth of 60 months of age around the age-65 threshold in our baseline regression (persons aged 60 to 70 years) and checked robustness to using alternative bandwidths. Our regressions weighted each month-of-age by month-of-event observation by the corresponding population. An illustrative observation is the hospitalization rate in March 2010 for persons born in June 1943. We computed SEs clustered on month of age to generate 95% CIs. Using these data, we estimate "reduced-form" regressions of the form:

$$Y_{mt} = \alpha_0 + \alpha_1 Z_{mt} + \alpha_2 \tilde{A}_{mt} + \alpha_3 \tilde{A}_{mt} Z_{mt} + \alpha_4 \tilde{A}_{mt}^2 + \alpha_5 \tilde{A}_{mt}^2 Z_{mt} + \delta_m + v_{mt}$$

The dependent variable was the event rate in month t for persons born in month m. (To convert event counts [for example, the number of hospitalizations in month t for persons born in month m] to event rates, we divided by the estimated number of persons born in month m and living in month t using census data. We then multiplied by 12 × 10 000 so that rates represented yearly hospitalizations per 10 000 persons.) Z_{mt} was an indicator for whether persons born in month m were aged 65 years or older by the vaccination deadline corresponding to month t. $\tilde{A}_{mt}$ was the running variable, or the age in month t for persons born in month m, normalized such that $\tilde{A}_{mt} = 0$ when persons born in month m were exactly 65 years old by the vaccination deadline corresponding to month t. The coefficient of interest, α_1, represents the reduced-form effect of the vaccination guidelines on the event rate Y_{mt}. Our regressions weighted each observation by the population of persons born in month m and alive in month t, and we included month-of-birth effects, δ_m, for additional precision.

We identified τ, the effect of vaccination on outcome Y, by combining the first-stage and reduced-form results. Specifically, we divided the effect of turning 65 on outcome Y, or α_1, by the effect of turning 65 on vaccination status, D, or θ_1.

$$\tau = \alpha_1 \div \theta_1$$

This strategy was analogous to using the age-65 discontinuity as an instrument to identify the causal effect of vaccination. In this case, we estimated α_1 and θ_1 using separate samples, which is equivalent to a 2-sample instrumental variables design. We computed SEs for the ratios with the delta method. We transformed the coefficients to percentage terms relative to the baseline rate of hospitalizations at age 64 years to calculate vaccine effectiveness and 95% CIs (see following section for details).

Calculation of Attack Rates

The effectiveness rates computed in randomized controlled trials and studies with cohort, case–control, and difference-in-differences designs is the difference in the event rates between the treatment and control groups divided by the control group event rate.

$$Effectiveness = (Rate_{Control} - Rate_{Treat}) \div Rate_{Control}$$

In this context, *Rate* represents hospital admission rates or death rates.

In our study, raw hospitalization rates at age 64 years may not represent the true hospitalization rates for untreated persons—the benchmark used in other studies—because approximately 50% of persons aged 64 years are vaccinated. This distinction is irrelevant when rescaling our point estimates because the point estimates imply that vaccination does not affect the outcomes. It becomes important when computing CIs, however, because the CI boundaries may correspond to nontrivial vaccination effects. Effects of this size imply that the age-64 hospitalization rate underestimates the true hospitalization rate for untreated persons in this age range. To preserve the duality between CIs and hypothesis tests, at the CI edges we used the procedure described in the following paragraphs to rescale the age-64 event rates. Without this rescaling, the 95% CI edges could not be interpreted as $\alpha = 0.05$ tests of the null hypothesis that the vaccine's effectiveness is equal to the value at the CI edge.

We begin by noting that the fuzzy regression discontinuity design generates an estimate of the difference in event rates between the treated and control groups due to vaccination. This difference is denoted by τ, where $\tau = Rate_{Treat} - Rate_{Control}$. To estimate τ, we divided the change in hospitalization or mortality rates at age 65 by the change in vaccination rates at age 65 (see equation earlier).

The hospitalization and mortality rates in the treatment group are a function of the attack rate in the treatment group, denoted by A_T, and the vaccine effectiveness (the proportion of influenza hospitalizations and deaths that the vaccine protects against), denoted by V. Thus $Rate_{Treat} = A_T \times (1 - V_T)$ and $Rate_{Control} = A_C$. In a randomized controlled trial, randomization ensures that the treatment and control groups have similar attack rates (that is, $A_T = A_C$). These expressions clarify that, if the vaccine has any effectiveness against influenza, the observed hospitalization and mortality rates in the treatment group underestimate the attack rates. Randomized controlled trials thus normalize by the control group rates, rather than the overall rates, when effectiveness is computed.

If no one younger than 65 years were vaccinated, we could use the raw hospitalization or mortality rates for those just under age 65, $Rate_{\uparrow 65}$, to estimate $Rate_{Control}$. In our context, however, a large share of persons just under age 65 are vaccinated (49.8%, per **Supplement Table 2**). $Rate_{\uparrow 65}$ thus underestimates $Rate_{Control}$, assuming that the vaccine has any effectiveness. To reconstruct the hospitalization and mortality rates below age 65 years, we exploit the fact that the attack rate for treated (vaccinated) persons, A_T, is their observed rate minus the treatment effect—that is, $A_T = Rate_{Treat} - \tau_T$. The attack rate for control (unvaccinated) persons is, by definition, $A_C = Rate_{Control}$. Let P_T and P_C represent the proportions of treated and control persons, respectively. We can express the attack rate just below age 65 years as a weighted average:

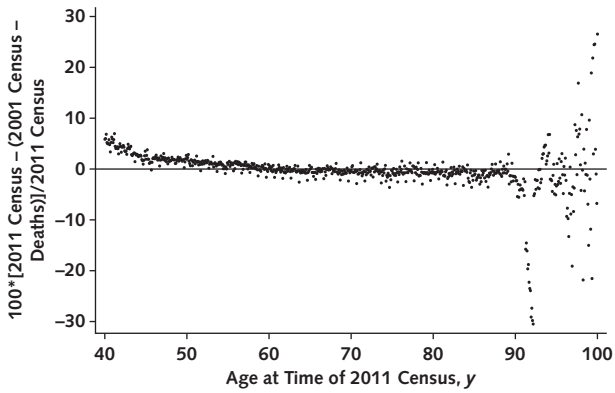
$$A_{\uparrow 65} = P_T(Rate_{Treat} - \tau_T) + P_C Rate_{Control}$$
$$= (P_T Rate_{Treat} + P_C Rate_{Control}) - P_T\tau_T$$
$$= Rate_{\uparrow 65} - P_T\tau_T$$

This expression suggests a simple way to estimate the attack rate at age 65 years: Take the hospitalization or mortality rate below age 65, $Rate_{\uparrow 65}$, and subtract the treatment effect estimate multiplied by the proportion of treated persons below age 65, $P_T\tau_T$. This calculation requires the assumption that the treatment effect is similar for treated persons younger than and older than 65 years, but we need this assumption regardless to generalize the estimates.

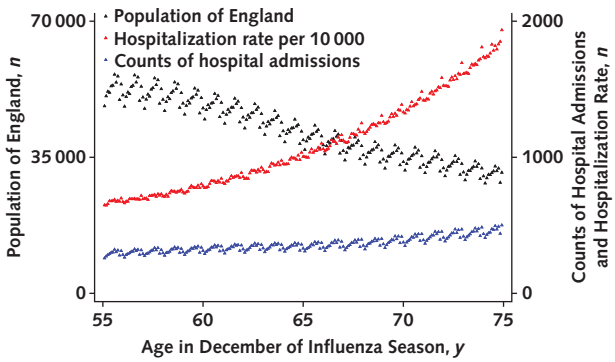
Appendix Table. Summary of Hospital Admission Types

Admission Type	Total Observations, *n*	Influenza, *n*	Pneumonia and Influenza, *n*	Respiratory, *n*	Circulatory, *n*
Primary cause of admission					
Admission	146 327 850	25 673	1 394 095	7 748 523	11 156 101
Ordinary admissions	87 520 312	25 448	1 380 560	7 188 577	7 681 902
Emergency admissions	49 105 923	24 485	1 354 230	6 003 755	5 864 884
Anywhere on admission record					
Admission	146 327 850	37 710	2 107 357	17 120 912	31 134 522
Ordinary admissions	87 520 312	36 213	2 086 153	14 105 929	21 541 385
Emergency admissions	49 105 923	32 240	1 984 969	11 082 872	16 203 271

Appendix Figure 1. Comparing 2011 census with estimate.



Appendix Figure 2. Effect of population denominators.



Web-Only Reference

42. U.S. Census Bureau. Methodology for the intercensal population and housing unit estimates: 2000 to 2010. October 2012. Accessed at www2.census.gov/programs-surveys/popest/technical-documentation/methodology/intercensal/2000-2010-intercensal-estimates-methodology.pdf on 14 December 2016.