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The association between influenza vaccination uptake and influenza and pneumonia-associated deaths in the United States

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ABSTRACT

Background: The influenza mortality burden has remained substantial in the United States (US) despite relatively high levels of influenza vaccine uptake. This has led to questions regarding the effectiveness of the program against this outcome, particularly in the elderly. The aim of this evaluation was to develop and explore a new approach to estimating the population-level effect of influenza vaccination uptake on pneumonia and influenza (P&I) associated deaths.

Methods: Using publicly available data we examined the association between state-level influenza vaccination and all-age P&I associated deaths in the US from the 2013–2014 influenza season to the 2018–2019 season. In the main model, we evaluated influenza vaccine uptake in all those age 6 months and older. We used a mixed-effects regression analysis with generalised least squares estimation to account for within state correlation in P&I mortality.

Results: From 2013–2014 through 2018–2019, the total number of all-age P&I related deaths during the influenza seasons was 480,111. The mean overall cumulative influenza vaccine uptake (age 6 months and older) across the states and years considered was 46.7%, with higher uptake (64.8%) observed in those aged $\geq$ 65 years. We found that overall influenza vaccine uptake (6 months and older) had a statistically significant protective association with the P&I death rate. This translated to a 0.33 (95% CI: 0.20, 0.47) per 100,000 population reduction in P&I deaths in the influenza season per 1% increase in overall influenza vaccine uptake.

Discussion: These results using a population-level statistical approach provide additional support for the overall effectiveness of the US influenza vaccination program. This reassurance is critical given the importance of ensuring confidence in this life saving program. Future research is needed to expand on our approach using more refined data.

1. Introduction

Influenza infection results in substantial disease burden with estimates of average annual influenza deaths of between 291,000 to 646,000 globally [1]. In the United States (US), influenza mortality remains high with annual estimates of influenza death particularly elevated in the elderly aged over 65 years [2]. This substantial influenza mortality burden has persisted in the US despite recommendations for influenza vaccination for all individuals over the age of 6 months (who do not have contraindications) and relatively high levels of influenza vaccine uptake, which has been approximately 50% in those aged 6 months over the last decade and higher in those aged over 65 years [3], who are most at risk of influenza death [4].

Systematic reviews of the available clinical trial evidence have estimated that influenza vaccination offers protection against influenza infection [5–7]. Likewise, observational case test-negative design studies in the US have shown protection against medically attended illnesses [8]. However, the assessing the evidence for the vaccine

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efficacy against the prevention of influenza mortality is more complex with clinical trials not powered to detect this relatively rare outcome [5]. This has led to questions regarding the evidence for the prevention of influenza mortality in the elderly [5,9]. While it is logical to assume that if a vaccine prevents infection and illnesses in an individual, it prevents subsequent consequences from infection (including influenza death) [10], those at highest risk of influenza mortality (e.g. frail elderly), may also be less likely to respond to influenza vaccination [11].

Population-level (ecological) observational analyses of US vital statistics have found it difficult to establish a substantial decline in influenza-related excess mortality coinciding with the increase in influenza vaccine uptake in the elderly [12]. Similar findings have been reported in Italy [13]. Estimating the population-level impact of influenza is complicated by seasonal variation in population immunity to influenza, the severity of predominant circulating subtypes, and the vaccine match to the circulating strains. Deaths that are due to influenza are also difficult to estimate due to non-specific clinical symptoms (e.g. pneumonia) and a lack of routine laboratory testing for influenza. This has led to the use of statistical methods to estimate the influenza burden from broader categories, such as pneumonia and influenza (P&I) deaths [2].

Analyses using mechanistic modelling approaches have continued to predict that current influenza vaccination substantially reduces influenza mortality in the US, with most prevented deaths from vaccination in the elderly [4,14]. However, the uncertainty raised about the vaccine efficacy against influenza mortality in the elderly has meant that new approaches to analysing the population-level impact of influenza vaccination are needed. Further analysis of the population effects of influenza vaccination are also timely given the emergence of high-dose and adjuvanted influenza vaccines with potential for higher efficacy [15].

The aim of this evaluation is to develop and explore a new approach using routinely collected state-level P&I mortality surveillance data in the US to estimating the population-level effect of influenza vaccination uptake on P&I mortality. The availability of state-based data, combined with high heterogeneity in vaccine coverage between US states, provides an important opportunity to evaluate the impact of influenza vaccination, which is not possible using publicly accessible data in many other countries.

2. Methods

We conducted a state-level retrospective observational study using publicly available data to assess the impact of seasonal influenza vaccine uptake on P&I associated deaths from the 2013–2014 influenza season through to the 2018–2019 influenza season. In the main model (M1), we assessed the impact of the overall influenza vaccine program using uptake in those age 6 months and older. In a secondary analysis, model 2 (M2), we evaluated vaccine uptake in 6 months-17 years and $\geq$ 65 years to estimate how each impacted on all-age P&I mortality in the influenza season.

3. Data and variables

3.1. Pneumonia and influenza (P&I) deaths

We accessed weekly P&I mortality data from the National Center for Health Statistics (NCHS) Mortality Surveillance System via the FluViewInteractive dashboard [16]. We examined all-age weekly P&I deaths. Age stratified data for states was not available in the dashboard. We started from the 2013–2014 season as this was the first season available in the dashboard. As SARS-CoV-2 began to circulate during the end of the 2019–2020 season in the US, we excluded this season. The P&I deaths are classified by the NHCS using the International Classification of Diseases (ICD)-10 codes and included deaths with any P&I diagnosis (J09-J18) within *multiple cause of death codes* (i.e., any field on the death certificate) [16].

In the US, seasonal influenza activity usually starts to rise in October and declines before late May [17]. We investigated P&I mortality during the period from December to March, the period when influenza activity is typically highest in the US [17]. We aggregated weekly P&I deaths for each state, from surveillance week 48 to week 13 (December to March) to form the state-level time series of P&I deaths across seasons. In the models, we used the P&I death rate per 100,000 population (i.e., P&I deaths divided by state population size multiplied by 100,000) in each influenza season (December to March).

3.2. Seasonal influenza vaccine uptake

We accessed influenza vaccine uptake from the US from the National Immunization Survey-Flu (NIS-Flu) and the Behavioral Risk Factor Surveillance System (BRFSS) via the FluVaxView dashboard [3]. For each state, the annual cumulative vaccination uptake (prevalence) was used. In addition to evaluating overall uptake (age 6 months and older) in our main analysis M1, we also stratified the vaccine uptake data into the following age groups: 6 months-17 years, 18–64 years, and $\geq$65 years. However, the initial correlation analysis showed that the time series of vaccine uptake in 18–64 year-olds was strongly associated with that of $\geq$65 year-olds. To avoid collinearity in these model independent variables, we excluded uptake in 18–64 year-olds from M2 and we evaluated vaccine uptake in 6 months-17 years and $\geq$65 years old populations. These were also the age groups where influenza vaccination uptake was seen as most likely to impact on population-level P&I deaths, via direct protection in the elderly or indirect herd protection from vaccination in school age children [18,19].

3.3. Seasonal influenza vaccine effectiveness against medically attended influenza

Estimates of all-age seasonal influenza vaccine effectiveness (all vaccine types) against medically attended influenza A or B infection were obtained from US Centers for Disease Control and Prevention (CDC) estimates [8]. This vaccine effectiveness (%) estimate, provided at the national level for each season, accounts for year-to-year variation in the vaccine effectiveness due to the match between the strains included in the vaccine and the circulating influenza strains in the US.

3.4. Population size

The estimated state-level mid-year population for each season were obtained from the US Census Bureau [20,21] to calculate the P&I death rate per 100,000 population and determine the proportion of persons aged 65 years and older for each year and state. The latter proportion was used to adjust for differences in population age between states and seasons.

3.5. Meteorological data

For each season and state, the average temperature (°F) from December through March was obtained to account for climatic variation that may influence P&I deaths [22].

3.6. Socioeconomic status

We used state-level poverty rate (i.e., % of the population below the poverty line) for each season from the Small Area Income and Poverty Estimates Program (SAIPE) of the US Census Bureau [23] to account for differences in standard of living between states by year.

3.7. Ethnic origin and race

To help account for differences in the ethnic and racial distribution of

the population between states we used the estimated Black and Hispanic population proportions from the US Census Bureau population data for each state and season [24].

3.8. Data pre-processing

As the population sizes and poverty rates were provided in calendar years, the corresponding data for a given year were matched with those data provided by influenza season that coincided with the same year spanning January through March. For the state of New Jersey and District of Columbia, BRFSS interviews were not conducted for the 2018–2019 influenza season [25] so we used the average vaccine uptake between the previous and the subsequent seasons to fill in the missing figures. We also used the temperature record for the Honolulu airport [26] as a proxy measure of temperature for the state of Hawaii.

4. Statistical methods

We examined the association between state-level influenza vaccination and P&I deaths in the US across seasons using mixed-effects regression analysis (with an identity link) with generalised least squares estimation to account for within state correlation in P&I mortality. The main regression model (M1) was formulated as follows:

$$Y_{it} = \beta_0 + \sum_{j=1}^{8} \beta_j X_{j_{it}} + \alpha_i + \epsilon_{it}, i = 1, \cdots, 51 \text{ and } t = 1, \cdots, 6$$

where Y_{it} is the dependent variable that represents the P&I death rate per 100,000 population for the season t and state i, X_{1it} is the overall cumulative vaccine uptake (%) for state i and season t, α_i is the random-effects term that accounts for dependency in P&I mortality within state i, and ϵ_{it} is the error term. The other independent variables, $X_{j_{it}}, 2 \leq j \leq 8$, are the estimate of seasonal influenza vaccine effectiveness, the proportion of $\geq$ 65-year-olds in the population, average temperature from December to March, poverty rate, year, and Hispanic and Black population proportions. The parameter β corresponds to the coefficient of each independent variable. Another variant of the model (M2) was examined by replacing the overall cumulative vaccine uptake variable with the cumulative vaccine uptake variables for people aged 6 months to 17 years and $\geq$ 65 years.

To compare the two models, the model was refitted with a maximum likelihood estimation method rather than generalised least squares to enable comparison with likelihood ratio tests (if nested), Akaike's Information Criteria (AIC) and Bayesian Information Criterion (BIC). For each model, we obtained the coefficient for the vaccine uptake parameter to provide an estimate of the change in the rate of P&I deaths per 100,000 in the influenza season for every 1% change in the vaccine uptake (overall and age-specific). We then converted it to the estimated annual average total number of P&I deaths avoided for each 1% increase in vaccine uptake across the study period by multiplying the coefficient for the vaccine uptake parameter by the mean total population across all seasons (divided by 100,000). The 95% confidence intervals (CIs) were obtained similarly using the estimated lower and upper bounds of the regression coefficient for the vaccine uptake parameter.

To help validate the approach in our main analysis we performed a negative control scenario analysis. In this analysis, instead of using the winter period we used a summer period (prior to the influenza season) and aggregated weekly P&I deaths for each state from May to August of each calendar year. In this summer period the influenza vaccine should not be effective at preventing deaths and there should not be a negative association between vaccine uptake and the dependent variable.

All analyses were conducted in Stata version 17.0 [27].

5. Results

From 2013–2014 through 2018–2019, the total number of all-age P&I deaths during the six influenza seasons was 480,111. The mean P&I death rate per 100,000 population during the influenza season was 26.50, which varied widely from 11.81 (Alaska, 2017–2018) to 48.67 (West Virginia, 2017–2018). The P&I death rate per 100,000 population was substantially higher in the 2014–2015 and 2017–2018 seasons when compared to the other seasons (Fig. 1). Summary statistics for each season can be found in the supplementary material (Table S3) and summary statistics for the variables used in the model in Table 1.

The mean overall cumulative influenza vaccine uptake (age 6 months and older) was 46.7%, which varied substantially depending on the state from 35.2% (Wyoming, 2017–2018) to 60.5% (Rhode Island, 2018–2019) (Table S1). There was some variation in annual uptake from season to season, with the lowest overall uptake in 2017–2018 (42.9%) (Fig. 2). The mean cumulative influenza vaccine uptake for those aged 6 months to 17 years was 59.5%, with a low of 41.7% (Wyoming, 2017–2018) and a high of 81.9% (Massachusetts, 2018–2019). For those aged $\geq$ 65 years, the mean cumulative influenza vaccine uptake was 59.5%, with a low of 49.9% (Wisconsin, 2015–2016) and a high of 76.8% (North Carolina, 2014–2015 and South Dakota, 2015–2016).

Fig. 3 shows the overall predicted (from M1 and M2) and observed P&I death rate per 100,000 population fit of the models and demonstrate that both models show a good fit to the observed data. Based on the calculated AIC and BIC scores, M1 performs slightly better than M2 (Table S2).

In model 1 (M1), we found that overall influenza vaccine uptake (6 months and older) had a statistically significant negative (protective) association with all-age P&I death rate per 100,000 (Table 2). This translated to a 0.33 (95% CI: 0.20, 0.47) per 100,000 population reduction in P&I deaths in the influenza season per 1% increase in overall influenza vaccine uptake, which was equivalent to preventing an average annual of 1083 (95% CI: 656, 1509) P&I deaths in the US.

In model 2 (M2), we found that influenza vaccine uptake in $\geq$ 65-year-olds had a statistically significant negative (protective) association with the all-age P&I death rate per 100,000 (Table 2) but that there was no statistically significant association for influenza vaccine uptake in those aged 6 months-17 years (0.04; 95% CI: −0.07, 0.16). For influenza vaccine uptake in $\geq$ 65 years, this result translated to a 0.17 (95% CI: 0.08, 0.27) per 100,000 population reduction in P&I deaths in the influenza season per 1% increase in influenza vaccine uptake in the elderly, which was equivalent to preventing an average annual of 561 (95% CI: 243, 871) P&I deaths in the US.

For the other independent variables (in M1 and M2), we found a statistically significant positive (enhancing) association between the P&I death rate per 100,000 population and poverty rate and proportion of $\geq$65 year-olds and a statistically significant negative association with vaccine effectiveness, year, and Hispanic and Black population proportions (Table 2). There was a negative trend in mortality over time, while temperature was not associated with mortality.

The negative control scenario analysis found a small positive (enhancing) effect from vaccination uptake on mortality during summer months (Table S4) which was only statistically significant in M1. As the negative control did not find a protective effect in summer, it adds reassurance that the main model is not biased towards overestimating the effects of influenza vaccination.

6. Discussion

Using population-level data from 2013–2014 to 2018–2019, we found that overall influenza vaccine uptake had a significant protective association with the P&I death rate in our main analysis (M1). In our secondary analysis (M2), we found a similar association for influenza vaccine uptake in $\geq$65-year-olds but no statistically significant association for influenza vaccine uptake in those aged 6 months-17 years. These results provide support for the overall effectiveness of the US influenza vaccination program and the direct protection offered by influenza vaccination of the elderly. The results for children in the US

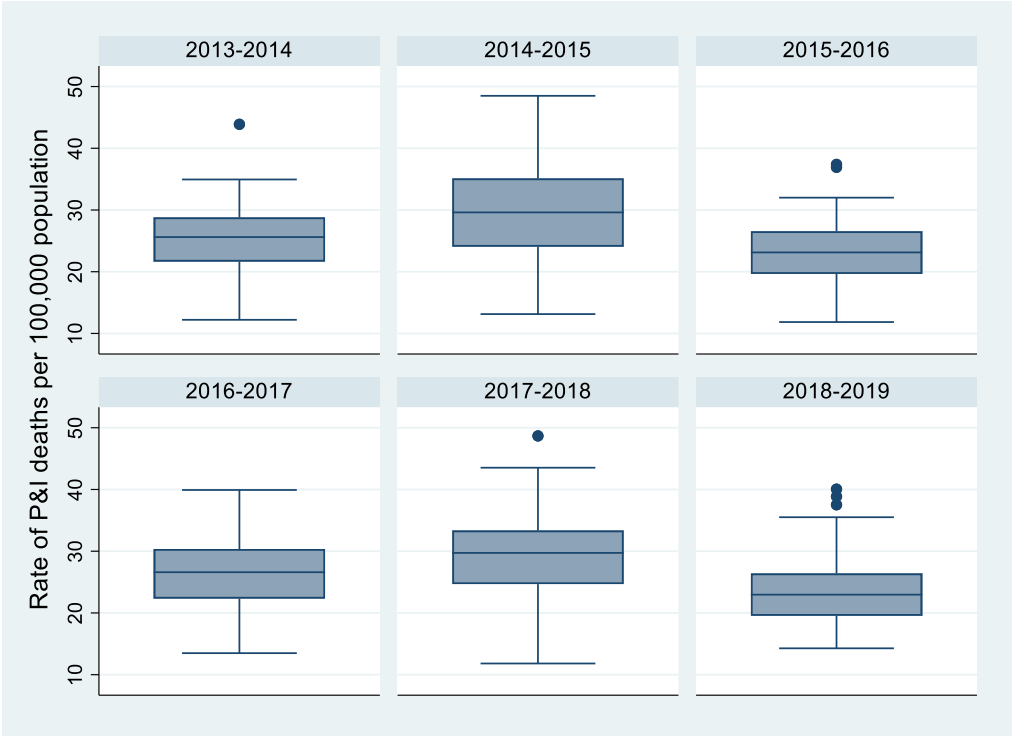

Fig. 1. Boxplot of the pneumonia and influenza (P&I) death rate per 100,000 population during the influenza season across all states for each season, 2013–2014 through 2018–2019.

Table 1
Summary statistics of the variables used in the model, overall, 2013–2014 through 2018–2019, United States.

Variable	Mean	Standard deviation	Minimum	Maximum
P&I deaths during the influenza season	1568.99	1649.47	87.00	10691.00
Population size	6,347,998	7,186,723	579,054	39,400,000
P&I death rate per 100,000 population	26.50	6.85	11.81	48.67
Overall vaccine uptake (%), 6 months and older	46.68	5.01	35.20	60.50
Vaccine uptake in 6 month-17-year-olds (%)	59.52	7.55	41.70	81.90
Vaccine uptake in ≥ 65-year-olds (%)	64.81	5.71	45.10	76.80
Temperature (°F)	35.72	12.63	5.55	75.70
Poverty rate (%)	13.46	3.03	7.50	22.10
Proportion of ≥ 65-year-olds	0.16	0.02	0.10	0.21
Vaccine effectiveness (%)	37.67	11.13	19.00	52.00
Hispanic population proportion	0.12	0.10	0.01	0.49
Black population proportion	0.12	0.11	0.01	0.49

Notes:
P&I, pneumonia and influenza.
Values for P&I deaths, P&I death rate per 100,000 population, and temperature were obtained using data from December to March.

may reflect the lower risk of death from influenza particularly in older children relative to overall all-age P&I deaths [2].

The significant associations for other variables included in the models were generally consistent with the existing evidence, with higher poverty rates [28] and proportion of ≥65-year-olds [4] being associated with increased P&I death rates per 100,000 population and greater influenza vaccine effectiveness associated with lower rates. The results for Hispanic and Black population proportions contrasted with the existing evidence [29] and may reflect the limitations in the data used to incorporate ethnic origin and race in the analyses, which did not consider factors such as the age of the Black and Hispanic populations.

When we converted our results to estimate the population-level change in P&I deaths per 1% increase in influenza vaccine uptake (in those age 6 months and older), the estimated impact on death was substantial, preventing 561 (95% CI: 243, 871) P&I deaths. Our analysis indicates significantly greater population-level effects from influenza vaccination than modelling previously estimated by the US CDC [4]. From 2013–2014 to 2018–2019, the US CDC estimated that approximately 6000 deaths were averted on average annually by influenza vaccination in the US [30]. We found that relatively modest changes in the current overall influenza vaccine uptake (or uptake in the elderly) may result in substantial changes in P&I associated deaths, suggesting that the influenza vaccination program may be more influential at a population level than previously estimated. A recent 2023 study has examined the impact of seasonal influenza vaccination on mortality in the elderly in Italy using a broadly similar approach to our study [31]. In this setting for those aged over 65 years they found that for every 1% increase in influenza vaccination uptake there was a 0.6% decrease in P&I mortality in that age group.

The discrepancies in estimates of the population level impact of influenza vaccination in the US produced using the US CDC approach when compared to our estimates may reflect the differences in the methods used. The US CDC takes a modelling approach that involves predicting what the influenza disease burden would have been if there

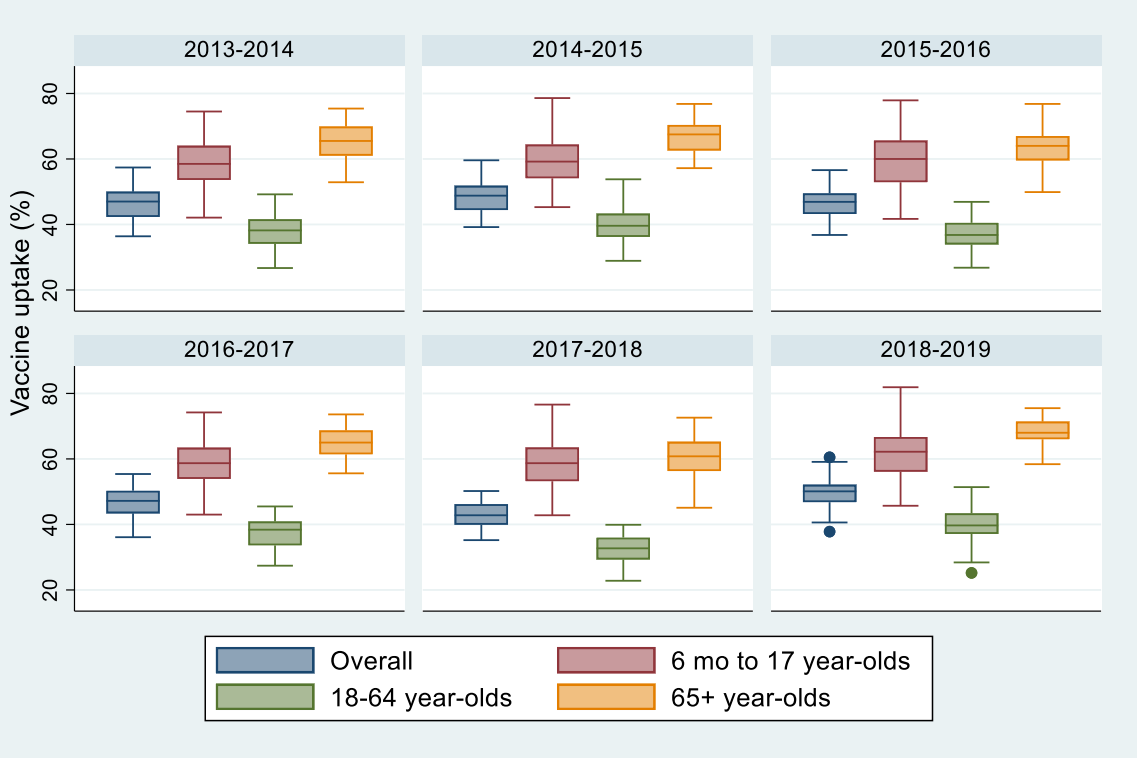

Fig. 2. Boxplot of the vaccine uptake (overall, age 6 months and older, and age-specific) across all states for each season, 2013–2014 through 2018–2019.

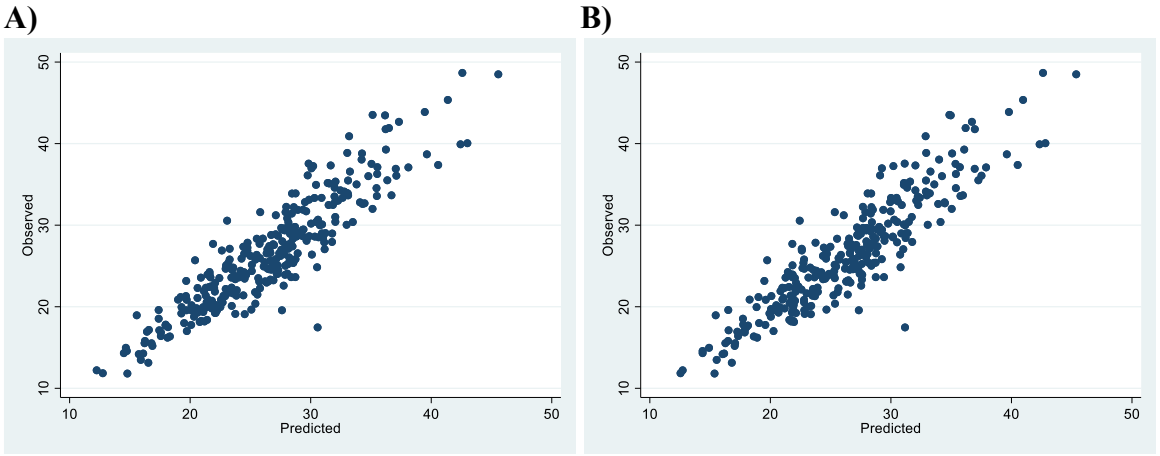

Fig. 3. Scatter plots of observed against predicted pneumonia and influenza (P&I) death rate per 100,000 population during the influenza season, 2013–2014 through 2018–2019. The subplot A correspond to M1, while the subplot B refers to M2. M1, overall vaccine uptake (age 6 months and older) as the main independent variable in the model; M2, vaccine uptake in those aged 6 months-17 years and ≥ 65 years old as main independent variables in the model.

had been no influenza vaccination using national estimates of the influenza burden, vaccination coverage and vaccine effectiveness [4]. Alternatively, our statistical approach leverages heterogeneities in vaccine uptake between US states to study the association between P&I death rates in the influenza season, influenza vaccination uptake and other factors. Each method has advantages and limitations, for example, the US CDC approach excludes herd protection from vaccination (which is implicitly included in our population-level ecological approach) and relies on the estimates of influenza disease burden used as inputs into the model being accurate. Even though our estimates of averted deaths seem high relative to these estimates, we ran a sensitivity analysis by applying our statistical model to summer mortality, a period when influenza does not circulate extensively in the US. We found a small positive effect of vaccination on mortality in this analysis (higher vaccine uptake increased summer mortality). While there could be trends in the state-level data that we cannot fully explain, we did not find evidence of a bias towards showing enhanced vaccine protection in our analysis.

One of the limitations of our analysis was that we used P&I death as our dependent variable, which includes all pneumonia deaths and is not specific to influenza. However, deaths coded specifically as influenza are known to underestimate the true influenza burden [2] and consequently the broader category of P&I death in *any field* on the death certificate also has advantages. To help address the non-specific nature of the variable we restricted our analysis to months when influenza was most likely to be circulating and causing deaths. While in theory we could have used excess mortality approaches to infer the contribution of influenza to P&I mortality (e.g. [2]), these approaches fail at the state-level due to small mortality counts. It would also be interesting for

Table 2
Association of influenza vaccine uptake with the per 100,000 population rate of pneumonia and influenza (P&I) deaths rate per 100,000 population (from December to March) controlling for other variables, from 2013–2014 through 2018–2019, United States.

Parameter	M1		M2	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Overall vaccine uptake (%), 6 months and older	−0.33 (−0.47, −0.20)*	<0.001	–	–
Vaccine uptake in 6 month-17-year-olds (%)	–	–	−0.04 (−0.16, 0.07)	0.462
Vaccine uptake in the ≥ 65-year-olds (%)	–	–	−0.17 (−0.27, −0.08) *	0.001
Vaccine effectiveness (%)	−0.18 (−0.22, −0.14) *	<0.001	−0.17 (−0.21, −0.13) *	0.000
Temperature (°F)	−0.02 (−0.10, 0.07)	0.705	−0.01 (−0.09, 0.07)	0.794
Poverty rate (%)	0.76 (0.35, 1.17) *	<0.001	0.86 (0.45, 1.28) *	<0.001
Proportion of persons aged 65 + years	105.90 (44.68, 167.11) *	0.001	105.22 (44.65, 165.78) *	0.001
Year	−0.62 (−1.07, −0.17) *	0.006	−0.56 (−1.00, −0.11) *	0.014
Hispanic population proportion	–22.31 (−34.15, −10.46) *	<0.001	−21.81 (–33.63, −9.98) *	<0.001
Black population proportion	−19.67 (–32.21, −7.14) *	0.002	−19.84 (–32.57, −7.11) *	0.002

Notes:
M1, Overall vaccine uptake (age 6 months and older) as the main independent variable (IV) in the model.
M2, Both vaccine uptakes in 6 months-17-year-olds and ≥ 65-year-olds as main independent variables in the model.
CI, confidence interval.
* Statistically significant at 0.05.

further research to explore the role of pneumococcal vaccination in the US and how this may interact with estimates for influenza mortality prevention using our approach. Another limitation is that we used all-age P&I death, as weekly age stratified data for states were not publicly available in the FluViewInteractive dashboard [16]. However, the purpose of this analysis was to establish the feasibility of a new approach to estimating the impact of influenza vaccination in the US and we hope that future analyses will expand on the approach using more refined data, such as age specific mortality data. The approach is only likely to be applicable to the US and other countries that have annual region specific data on influenza vaccination coverage, mortality related to influenza and other key variables.

We believe that the new approach established in this article provides support for the overall effectiveness of the US influenza vaccination program and that the methods will be useful in better understanding the population-level effect of influenza vaccination uptake in the US.

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CRediT authorship contribution statement

Anthony T. Newall: Methodology, Supervision, Writing – original draft, Writing – review & editing, Project administration, Conceptualization. **Allen L. Nazareno:** Formal analysis, Writing – review & editing, Data curation, Writing – original draft. **David J. Muscatello:** Writing – review & editing, Methodology. **David Boettiger:** Writing – review & editing, Methodology. **Cécile Viboud:** Writing – review & editing. **Lone Simonsen:** Writing – review & editing. **Robin M. Turner:** Formal analysis, Writing – review & editing, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The research uses public data

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Disclaimers

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US National Institutes of Health or Department of Health and Human Services.

The contents of the published material are solely the responsibility of the Administering Institution, a Participating Institution or individual authors and do not reflect the views of the NHMRC.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.01.089.

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