Estimation of Influenza Vaccine Effectiveness using Secondary Data: A Cohort Study and Propensity Score-Matched Analysis of Claims Data from Baden-Wuerttemberg

Schätzung der Wirksamkeit der Grippeimpfung anhand von Sekundärdaten: Eine Kohortenstudie und Propensity-Score-Matching-Analyse von Leistungsdaten aus Baden-Württemberg

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ABSTRACT

Our objective was to estimate and replicate influenza vaccine effectiveness (VE) for the 2014/2015 influenza season (IS) based on routine data from a German health insurance claims dataset. In addition, we investigated associated methodological aspects. From the AOK Baden-Württemberg, claims data of 2.64 million insured persons residing in Baden-Wuerttemberg and aged 15 years and older were available for analysis. Based on influenza vaccine-specific reimbursement codes claimed in the vaccination period of 2014, participants were classified as either vaccinated or unvaccinated. Baseline covariates that could confound the association between vaccination and influenza infection were considered for all participants. Covariates included age, sex, place of residence, and covariates indicative of health status and health-service utilization. The primary outcome was defined as influenza hospitalization during the IS in winter and spring of 2015. Secondary outcomes included pneumonia hospitalizations, and all-cause mortality among others. Propensity score matching (PSM) was used to build a comparable set of vaccinated and unvaccinated participants. A bias analysis was conducted by estimating VE pre- and post-IS, periods in which vaccination is not thought to be effective, because influenza is not circulating in the population. A subset

of 839,706 participants could successfully be matched with a 1:1 ratio. The estimated influenza VE (based on influenza hospitalization) was 27 % [95 % confidence interval (CI): 17 %; 36 %], which compares well with the estimate of the RKI for the same season (27 % [95 % CI: -1 %; 47 %]). Bias analysis revealed that result could be partially accounted for by residual confounding yielding a potential overestimation of the true underlying effect. Secondary outcomes for pneumonia hospitalizations and mortality showed similar results though likely prone to a greater extent of residual confounding. It can be concluded that (1) secondary data from German health insurances can be used to derive plausible influenza VE estimates, and (2) PSM is a useful and transparent method to derive those estimates. In addition, (3) residual confounding is a relevant problem in observational studies on VE and (4) bias analysis in pre- and post-season periods are an essential complement for interpretation of results.

ZUSAMMENFASSUNG

Ziel war es die Wirksamkeit der Influenza-Impfung (VE) für die Grippesaison 2014/2015 auf Grundlage von Routinedaten aus Krankenkassendatensatz zu schätzen und zu replizieren. Zusätzlich sollten methodische Aspekte untersucht werden. Es wurden Abrechnungsdaten von 2,64 Millionen Versicherten der AOK Baden-Württemberg mit dortigem Wohnsitz ab 15 Jahren analysiert. Basierend auf Abrechnungsdaten für die Influenza-Impfung 2014, wurden die Teilnehmer als ungeimpft oder geimpft klassifiziert. Kovariablen, die den Zusammenhang zwischen Impfung und Influenzainfektion beeinträchtigen könnten, wurden berücksichtigt. Hierzu gehörten Alter, Geschlecht, Wohnort sowie Kovariablen, die auf den Gesundheitszustand und die Inanspruchnahme von Gesundheitsdienstleistungen hinweisen. Der primäre Endpunkt war ein Krankenhausaufenthalt wegen Influenza während der Grippesaison 2015. Zu den sekundären Endpunkten gehörten unter anderem Krankenhausaufenthalte wegen Lungenentzündung und die Gesamtmortalität. Um eine vergleichbare Gruppe von geimpften und ungeimpften Teilnehmern zu ermitteln, wurde ein Propensity-Score-Matching (PSM) durchgeführt. Es wurde eine Bias-Analyse durchgeführt, bei der die VE vor und nach der Grippesaison geschätzt wurde, also zu Zeitpunkten, in denen angenommen wurde, dass die Influenza nicht in der Bevölkerung zirkulierte und die Impfung nicht wirken konnte. Insgesamt konnten 839.706 Teilnehmer 1:1 gematcht werden. Die geschätzte VE (basierend auf Influenza bedingten Krankenhausaufenthalten) betrug 27 % [95 %Konfidenzintervall (KI): 17 %; 36 %], was der Schätzung des RKI für dieselbe Saison (27 % [95 %KI: -1 %; 47 %]) entspricht. Die Bias-Analyse zeigte, dass das Ergebnis teilweise durch residuale Konfundierung erklärt werden kann, was zu einer potenziellen Überschätzung des zugrunde liegenden Effekts führt. Die Ergebnisse der sekundären Endpunkte zeigten ähnliche Ergebnisse, obwohl sie wahrscheinlich in höherem Maße durch residuale Konfundierung bedingt sind. Zusammenfassend zeigt sich, dass (1) sekundäre Daten der deutschen Krankenkassen verwendet werden können, um plausible VE-Schätzungen abzuleiten, und dass (2) das PSM eine nützliche und transparente Methode zur Ableitung dieser Schätzungen ist. Darüber hinaus ist (3) residuale Konfundierung ein relevantes Problem in Beobachtungsstudien zu VE und (4) Bias-Analysen vor- und nach der Grippesaison sind eine wesentliche Ergänzung für die Interpretation der Ergebnisse.

Introduction

Influenza vaccines are a preventive technique that only induce temporary and partial immunity. Therefore, new vaccine formulations are issued yearly, accompanied by vaccine effectiveness (VE) studies. Such studies mostly use a test-negative design, a study design derived from case-control studies.

In observational studies, the comparability of relevant characteristics between vaccinated and unvaccinated individuals cannot be assumed and an unadjusted comparison will likely be biased. Two major sources of bias are confounding by indication and bias by health care-seeking behavior. As influenza vaccination is indicated in high-risk groups this clearly leads to vaccinated persons being – on average – older and more frequently diseased. Bias by health care-seeking behavior is introduced if persons who seek vaccination have a different risk of the outcome than unvaccinated persons. Studies so far have shown strong evidence of relevant bias indicating vaccinated persons to be generally healthier than unvaccinated persons [1, 2].

With the increasing availability of large electronic health-care data, interest in its use for VE studies arose. The use of German health-insurance claims data for influenza VE estimation has not been investigated so far. The primary aim of this study was to estimate and replicate influenza VE for the 2014/2015 influenza season based on routine data from a German health insurance's claims dataset. In addition, secondary objectives addressed the investigation of associated methodological aspects. Therefore, we examine the advantages and disadvantages of using secondary data and propensity score matching models (PSM) in VE research.

Methods

Study design, setting and participants

A retrospective cohort study was performed comparing influenza-related outcomes in participants that were either vaccinated against seasonal influenza or not. The primary outcome is hospitalization with confirmed influenza.

Individual participant information was obtained from the AOK (Allgemeine Ortskrankenkasse) Baden-Württemberg, a large German statutory health insurance fund, covering a total of about 3.8 million insured individuals. The study was conducted according to the "Good Practice of Secondary Data Analysis" [3]. Routine data of German health insurances can be used for scientific purposes, as regulated in the German social code book V (§303e). This study

was embedded in a larger scientific program that evaluated the General Practitioner-Centered Care (German: Hausarztzentrierte Versorgung) program in Baden-Wuerttemberg, conducted by the the Institute of General Practice of the Goethe-University in Frankfurt/Main. For this evaluation there were no concerns by the Ethics Committee of the Goethe-University (Medical Faculty, No. 470/13).

As the study aims to estimate the influenza VE of the influenza season 2014/2015, exposure was assessed in 2014 and the main outcomes in 2015. According to the RKI, the influenza season occurred between the 2nd and 16th calendar week of 2015 [4]. During this period the occurrences of the main outcomes were assessed. Influenza vaccination usually does not start before August and most vaccinations are done by end of December. Because the antibody development after influenza vaccination takes about two weeks [5, 6], all participants who had an influenza vaccination recorded between August 1, 2014 and December 18, 2014 were considered to be effectively vaccinated.

Participants were eligible for inclusion given a minimum age of 15 years (to reflect the age groups of the RKI's annual influenza reports) and current residency in Baden-Wuerttemberg (according to their zip-code). To ensure completeness of covariate and exposure information, participants had to be insured from January 2013 until December 2014. To avoid exposure misclassification of the unvaccinated group, all participants with a vaccination against influenza between December 23, 2014 and June 30, 2015 were excluded from analysis.

Exposure and outcomes

All participants having had at least one of the three influenza vaccination codes (89111, 89112, 89133) recorded between August 1 and December 22, 2014 were classified as exposed. If more than one vaccination was coded, the date of the earlier dataset entry was used.

Diagnoses of patients admitted to a hospital are coded using ICD-10. Only confirmed outpatient diagnoses were considered. All outcomes were coded as binary variables. For hospital diagnoses, the date of the corresponding hospital admission was recorded. For patients that had multiple occurrences of the outcome, the first was considered. All outcomes by date were assessed between January 5 and April 19, 2015. Outpatient diagnoses are only exact to the quarter of each year. Therefore, all coded outpatient cases during the first quarter of the year 2015 were recorded.

The primary outcome of this study is hospital admission with influenza as primary hospital diagnosis during the influenza season of 2015. Secondary outcomes are (no. 1) hospital admission with influenza as primary hospital diagnosis or pneumonia as primary hospital diagnosis with influenza as secondary hospital diagnosis, (no. 2) hospital admission with pneumonia as primary diagnosis, (no. 3) outpatient diagnosis of influenza, (no. 4) outpatient diagnosis of acute respiratory tract infection and (no. 5) all-cause mortality during the influenza season of 2015 (▶ **Table 1**). Time of death is exact to the calendar month only. All deaths that occurred clearly within the influenza season were considered for this outcome. The following predefined subgroup analyses were conducted: all participants between ages of ≥ 15 and ≤ 59 years; all participants of age ≥ 60 years.

Covariates

Multiple covariates were used to control for potential confounding. A list of covariates with a rationale for their inclusion is shown in Online-Supplement ▶ **Table 1**. State variables like the nursing-grade were collected from the 2014 data tables. Comorbidities and information on health-service utilization were collected from January 1, 2013 through June 30, 2014 (Online-Supplement ▶ **Table 2**). For identification all inpatient and outpatient diagnoses were used.

Bias analysis

Because infection with influenza virus outside of the season is very uncommon in temperate zones [7], we conducted a bias analysis aiming to estimate relative risks of the study outcomes before, during and after the influenza season from calendar weeks 2 through 16 of the year 2015 [1]. The post-season period was defined from

▶ **Table 1** Description of outcomes and ICD-10 codes used for their assessment.

Outcomes	Name	ICD-10-GM 2015	Timeframe
Primary Outcome	**Hospital admission with influenza as primary hospital diagnosis**	**"J09", "J10"**	**Between January 5, 2015 and April 19, 2015**
Secondary Outcome #1	**Hospital admission with influenza as primary hospital diagnosis or pneumonia as primary hospital diagnosis with influenza as secondary hospital diagnosis**	**"J09", "J10", "J12", "J13", "J14", "J15", "J16", "J17", "J18"**	
Secondary Outcome #2	**Hospital admission with pneumonia as primary hospital diagnosis**	**"J12", "J13", "J14", "J15", "J16", "J17", "J18"**	
Secondary Outcome #3	**Outpatient diagnosis of influenza**	**"J09", "J10", "J11"**	**Because outpatient diagnoses are not exact to the date, all coded cases during the first quarter of the year 2015 were recorded.**
Secondary Outcome #4	**Outpatient diagnosis of acute respiratory tract infection**	**"J00", "J01", "J02", "J03", "J04", "J05", "J06", "J20", "J21", "J22", "J09-J18"**	
Secondary Outcome #5	**All-cause mortality**		**The data do not contain the cause of death and time of death is exact to the calendar month only. All deaths that occurred clearly within the influenza season (in February and March 2015) were recorded for this outcome.**

▶ **Table 2** Propensity score matching (PSM) treatment to balance the vaccinated and unvaccinated participants before and after matching (mean and standard deviation or percentage).

Demographic Characteristics	Before PSM			After PSM		
	V+	V-	SMD	V+	V-	SMD
N	424,436	2,201,414		419,853	419,853	
Age	69.87 (14.71)	48.85 (19.55)	1.215	69.74 (14.63)	69.74 (14.63)	<0.001
sex (male)	41 %	45.2 %	0.086	41.00 %	40 %	0.015
nationality (German)	90 %	82 %	0.218	90 %	90 %	0.014
nursing home residency	3 %	<1 %	0.222	3 %	2 %	0.071
hospital admissions	0.71 (1.57)	0.38 (1.11)	0.246	0.70 (1.42)	0.69 (1.35)	0.007
median	0	0	–	0	0	–
interquartile range	1	0	–	1	1	–
outpatient quarter-wise cases	16.15 (8.09)	10.51 (7.40)	0.728	16.07 (7.99)	15.81 (8.29)	0.032
median	15	9	–	15	15	–
interquartile range	10	9	–	10	10	–
respiratory disease	24 %	13 %	0.28	24 %	23 %	0.019
cardiovascular disease	41 %	13 %	0.66	41 %	40 %	0.007
diabetes mellitus	35 %	12 %	0.572	35 %	34 %	0.018
renal disease	15 %	4 %	0.389	15 %	14 %	0.025
hepatic disease	2 %	1 %	0.093	2 %	2 %	0.001
immunosuppression	1 %	1 %	0.049	1 %	1 %	0.009
neoplasm	18 %	7 %	0.354	18 %	18 %	0.004

V+: vaccinated participants, V-: unvaccinated participants; SMD: standardized mean difference.

calendar weeks 18 through 32 of the year 2015, with a one-week gap between the RKI-defined influenza season and the post-season period. The pre-season period was defined as calendar weeks 49 through 52 of the year 2014. As outpatient diagnoses are only exact to the quarter of the year, the first quarter of the year 2015 was defined as the in-season period and the third quarter of the year 2015 as the post-season period for outcomes no. 3 and no. 4. As the mortality data are only exact to the month of the year, the outcome of all-cause mortality used December 2014 as pre-season period, February and March 2015 as in-season period and the months from May until July as post-season period.

Statistical analysis

For descriptive analysis absolute and relative frequencies, mean and standard deviations were calculated.

The propensity score was calculated with a binary logistic regression model. The dependent variable was vaccination status, the independent variables were all covariates except age. Because of very long computing times, it was decided to do a stratified PSM for age. For the matching process, the dataset was stratified by yearly age groups and those of age > 90 years.

We used (greedy) nearest-neighbor matching and the ratio was 1:1. Matching was done without replacement and a caliper of 0.2 standard deviations of the distance measure was used.

To account for the matched nature of the dataset, the risk ratio (RR) was estimated as described by Austin [8]. Influenza VE studies often express their results as a percentage value of "vaccine effectiveness" calculated as $VE = (1 - RR) * 100$9, 10]. As the outcome event is relatively rare, in this study the Odds Ratio (OR) almost equals the RR.

Analyses were done with the statistical software R version 3.4.2 [11]. For data preparation the packages readr version 1.1.1 and dplyr version 0.7.4 were used. PSM was done with "MatchIt" version 3.0.2, comparison tables including standardized differences were created with the package "TableOne" version 0.9.3. Figures were created with the package "ggplot2" version 3.1.0.

Results

After application of exclusion criteria (Online-Supplement Figure 1) and accounting for 9,458 participants that received their first vaccination after the exposure period 2,625,850 participants remained. The mean age of participants was 53 years and 55 % were female (Online-Supplement ▶ **Table 3**). The comparison of the characteristics of vaccinated and unvaccinated participants before and after PS shows a good balance (▶ **Table 1**, **2**). It was possible to match 419,853 of the vaccinated participants. The remaining 4,583 (1.09 %) vaccinated participants were not matched.

The primary outcome occurred in 264 participants in the vaccinated group and in 364 participants in the unvaccinated group. This results in a decreased RR of 0.73 (95 %-CI: 0.64–0.83) in vaccinated individuals and a VE of 27 % (95 %-CI: 17–36 %)(▶ **Table 3**). Absolut numbers for hospitalizations and mortality are higher in the older age group, however, the RR for hospitalizations regarding influenza (no. 2) and mortality (no. 5) is similar in both age groups. Absolut numbers for outpatient diagnoses of influenza (no. 3) and respiratory tract infections (no. 4) are higher in the younger age group and the RR are lower than in the older group. The confidence intervals do not overlap.

▲ **Table 3** Results of the main analysis.

Outcome	All participants (N = 839,706)			Participants aged 15–59 years (N = 172,560)			Participants aged 60 years and above (N = 667,146)		
	Cases (N)		Risk Ratio [95 %-CI]	Cases (N)		Risk Ratio [95 %-CI]	Cases (N)		Risk Ratio [95 %-CI]
	V +	V-		V +	V-		V +	V-	
Primary	264	364	0.73 [0.63–0.83]	21	35	0.60 [0.38–0.96]	243	329	0.74 [0.64–0.85]
Hospital admission with influenza (no.1)	281	382	0.74 [0.64–0.84]	21	36	0.58 [0.37–0.93]	260	346	0.75 [0.65–0.86]
Hospital admission with pneumonia (no.2)	2,160	2,310	0.94 [0.89–0.98]	115	99	1.16 [0.92–1.46]	2,045	2,210	0.92 [0.88–0.97]
Outpatient diagnosis of influenza (No.3)	3,024	3,375	0.90 [0.86–0.93]	1,272	1,536	0.83 [0.78–0.88]	1,752	1,839	0.95 [0.90–1.01]
Outpatient diagnosis of acute respiratory tract infection (No.4)	56,419	55,425	1.02 [1.01–1.03]	19,317	20,448	0.94 [0.93–0.96]	37,102	34,977	1.06 [1.05–1.07]
All-cause mortality (No.5)	3,580	4,080	0.88 [0.84–0.91]	82	90	0.91 [0.7–1.18]	3,498	3,990	0.88 [0.84–0.91]

V + : vaccinated participants, V-: unvaccinated participants; CI: confidence interval.

▶ **Table 4** Results of the bias analysis: outcomes before (pre), during and after (post) influenza season (N = 789,970).

IS	Cases (N)		Risk Ratio [95 %-CI]
	V +	V-	
Primary			
Pre	1	5	0.20 [0.03–1.27]
Season	251	328	0.77 [0.66–0.88]
post	2	0	n/a
Hospital admission with influenza (no.1)			
pre	1	5	0.2 [0.03–1.27]
season	265	345	0.77 [0.67–0.88]
post	2	0	n/a
Hospital admission with pneumonia (no.2)			
pre	394	483	0.82 [0.73–0.91]
season	2,092	2,192	0.95 [0.91–1.00]
post	1,184	1,157	1.02 [0.95–1.10]
Outpatient diagnosis of influenza (No.3)			
season	2,831	3,226	0.88 [0.84–0.92]
post	537	417	1.29 [1.15–1.44]
Outpatient diagnosis of acute respiratory tract infection (No.4)			
season	52,838	52,045	1.02 [1.01–1.02]
post	16,566	15,361	1.08 [1.06–1.10]
All-cause mortality (No.5)			
pre	1,346	1,896	0.71 [0.67–0.75]
season	3,488	3,934	0.89 [0.85–0.92]
post	4,119	4,419	0.93 [0.90–0.97]

V + : vaccinated participants, V-: unvaccinated participants; CI: confidence interval; n/a: not applicable.

Bias analyses (▶ **Table 4**) for both primary and first secondary outcome show that influenza hospitalizations rarely occur at all before and after the season. Hospitalizations with pneumonia (no. 2) are more common during influenza season and bias analysis shows that vaccinated participants seem to have a lower RR of this outcome before the influenza season . After influenza season, their risk is almost equal to the risk in unvaccinated participants (RR 1.02; 95 %-CI 0.95–1.10).

A similar observation can be made for all-cause mortality (no. 5): the RR of mortality for vaccinated participants appears lower before the start of the influenza season than during the season. A weakened effect can be observed in the post-season.

The risks for outpatient diagnoses of influenza or acute respiratory infections are higher during the influenza season. The RR of vaccinated participants to have an outpatient diagnosis of influenza is lower during the influenza season, but is higher after the influenza season, with a RR of 1.29 (95 %-confidence interval (CI): 1.15–1.44).

Discussion

The estimated influenza VE for the season 2014/2015 is 27 % (95 %-CI: 17 % to 36 %). Our primary goal was to replicate the RKI VE for this season and our result is in line to the RKI estimate. [4]: 27 % (95 %-CI: -1 % to 47 %). While this study points towards higher

VE in the younger age group (RKI VE < 60 years: 17 % (95 %-CI -39 to 51 %) vs. our study VE < 60 years: 40 % (95 %-CI 4 to 62 %), the RKI's estimates show higher VE in the older age group (RKI VE ≥ 60 years 44 % (95 %-CI -8 to 71 %) vs. our study VE ≥ 60 years 26 % (95 %-CI 15 to 36 %).

There is a large debate on whether elderly people have a weaker immune response (and hence a lower VE) compared to younger persons [12, 13]. The wide confidence intervals in both studies are a limit to firm conclusions in this regard. Evidence from randomized controlled trials indicate that influenza vaccination has similar RR reductions in different age groups and absolute risk reduction is probably higher in older persons, due to their higher baseline risk [14, 15].

In addition to this baseline comparison, our examined secondary outcomes based on secondary data provide even more ways to assess VE. Hospital admission with influenza (no. 1) was rare and the outcome does not give any information in addition to the conclusions drawn from the primary outcome. Hospital admission with pneumonia (no. 2) occurred much more frequently than the primary outcome. Its RR of 0.94 shows that any possible effect of influenza vaccination on this outcome are smaller than on the primary outcome. This suggests that truly two different effects are measured and therefore secondary data studies on influenza VE should not use pneumonia hospitalizations or a composite of pneumonia and influenza hospitalizations as main outcome like older studies [1, 16]. Additionally, the effect estimate for prevention of pneumonia hospitalization by vaccination against influenza could plausibly be an artifact of residual confounding.

The estimated VE of 10 % for outpatient cases of influenza (no. 3) is lower than the estimate for the primary outcome. Possible explanations are related to misclassifications of outpatient diagnoses of influenza. Outpatient diagnosis of acute respiratory tract infection (no. 4) occurred with a marginally higher risk in vaccinated participants. RR was even higher after the influenza season further suggests that the outcome is biased. All-cause mortality (no. 5) seems to be lower in vaccinated compared to unvaccinated participants.

Concerning the outcomes pneumonia hospitalizations and all-cause mortality, the conducted bias analysis gives strong evidence for residual confounding in this analysis. It indicates an overestimation of VE, because RR for these outcomes are already lower before the beginning of the influenza season in vaccinated participants. This could be interpreted as healthy-vaccinee effect. Jackson and colleagues [1] observed that the RR were lower before the influenza season. The RR then became closer to the null value during and even more after the influenza season. They argue, since a protective effect of influenza vaccination should occur only within the influenza season, that this indicates relevant residual confounding.

Strengths and limitations

Among the major strengths of secondary data analysis is the potential for large sample sizes and sampling. The dataset is of good representativeness. Generally insured persons of the AOK tend to be somewhat older and of lower socio-economic status than the general population [17].

Another strength is the possibility to conduct a quantitative bias analysis. As the time of the influenza period is known, this allows assessing RR for the outcomes before and after the influenza period and thereby gains an impression of possible residual confounding.

The secondary outcomes have certain limitations that make interpretation difficult: they either seem to be biased or are unspecific about influenza infection. The strength of the primary outcome used, in contrast, is that it is both specific to influenza and clinically relevant.

One advantage of PSM is the possibility to conduct a balance analysis and compare vaccinated and unvaccinated regarding their baseline characteristics. The PSM worked very well as judged by the criterion of achieving a standardized difference of less than 0.1 for all covariates [18]. Possibilities for residual confounding remain, e.g., disease categories do not account for disease severity.

A further limitation is the lack of information on some potentially relevant confounders. Among the most relevant in this context are smoking status, frailty, occupation, socioeconomic status, and vaccinations by company physicians that are not transmitted to the health insurance company.

Generalizability

The aim of the study is to assess VE in a given influenza season in persons who typically receive a vaccination (i.e., who have an indication), and therefore the representativeness for vaccinated persons is very good, as almost all insured persons are available for analysis.

Conclusion

The objectives of the study were to estimate influenza VE based on claims data from Germany and to explore the performance of PSM. The main conclusion is that secondary data from German health insurances can be used to estimate influenza vaccine effectiveness that agree with results of other studies. Further conclusions are: (a) PSM is a useful and transparent method to derive those estimates, (b) residual confounding is a relevant problem in observational studies on VE and (c) bias analysis in pre- and post-season periods are an essential tool for interpretation of results.

Thus, by an additional evaluation of claims data, results could support the STIKO in identifying specific target groups recommended for vaccination. To further assess the validity of methods used, it would be essential to analyze additional seasons and compare estimates with those of different studies. A related aspect of gathering estimates across seasons is the possibility to further increase power for more specific subgroup analyses. Secondary data analyses could be especially useful for study questions on the waning of VE over time.

Conflict of Interest

The authors declare that they have no conflict of interest.

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