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Reduced Effectiveness of Repeat Influenza Vaccination: Distinguishing Among Within-Season Waning, Recent Clinical Infection, and Subclinical Infection

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Studies have reported that prior-season influenza vaccination is associated with higher risk of clinical influenza infection among vaccinees. This effect might arise from incomplete consideration of within-season waning and recent infection. Using data from the US Flu Vaccine Effectiveness Network (2011–2012 to 2018–2019 seasons), we found that repeat vaccinees were vaccinated earlier in a season by 1 week. After accounting for waning VE, we determined that repeat vaccinees were still more likely to test positive for A(H3N2) (odds ratio, 1.11; 95% CI, 1.02–1.21) but not influenza B or A(H1N1). We documented clinical infection influenced individuals' decision to vaccinate in the following season while protecting against clinical infection of the same type/subtype. However, adjusting for recent documented clinical infections did not strongly influence the estimated effect of prior-season vaccination. In contrast, we found that adjusting for subclinical or undocumented infection could theoretically attenuate this effect. Additional investigation is needed to determine the impact of subclinical infections on vaccine effectiveness.

Keywords. immunogenicity; infection block hypothesis; infection history; influenza vaccine; test negative design.

The World Health Organization recommends annual influenza vaccination of persons at high risk, with some countries recommending universal vaccination [1, 2]. A controlled study in the 1970s first raised questions about repeated annual influenza vaccination, reporting that prior vaccination indirectly increased the risk of infection in the current season [3, 4]. The phenomenon was not routinely investigated until a test-negative study in Canada [5], a vaccine trial in Hong Kong [6], and a household-based study in the United States [7] found differences in vaccine effectiveness (VE) and immunogenicity among repeat and nonrepeat vaccinees in the 2009–2010 and 2010–2011 seasons [8–14]. Since then, increased infection risk against A(H3N2) in repeat vaccinees was observed in multiple seasons and countries [7, 11, 12, 13, 15, 16], and it is less often reported for the less prevalent A(H1N1) and type B [8, 9]. The increased risk of infection in repeat vaccinees has been associated with lack of confirmed influenza infection in the prior season [17].

Test-negative studies conducted in health care settings have become the standard way to evaluate vaccine protection. A test-negative design estimates VE by comparing vaccination coverage in persons with medically attended acute respiratory illness who test positive vs negative for influenza [18]. Several factors that may bias estimates of repeat vaccination effects in a test-negative design have not been considered.

Vaccine-induced protection against influenza virus infection wanes within a season [19–23]. Consequently, the vaccine protection estimated among otherwise similar vaccinees may differ if the timing of vaccination is not considered. If repeat vaccinees tend to vaccinate substantially earlier in a season, waning protection could make the risk of infection among repeat vaccinees appear higher than in nonrepeat vaccinees. The rapidly changing risk of influenza incidence in a season may amplify the difference [24].

The infection block hypothesis [4, 25–27] suggests that prior vaccinations can block opportunities to experience immunogenic influenza virus infections, which can lead to more cross-reactive and durable immune responses than vaccination [28], especially when circulating viruses differ from vaccine strains [29, 30]. If true, the infection block hypothesis could explain the increased risk of infection among repeat vaccinees vs nonrepeat vaccinees: prior-season vaccination could protect repeat vaccinees against prior-season infection, leaving them with less

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immune protection at the start of an influenza season and hence a higher incidence of clinical infection in that season as compared with nonrepeat vaccinees. The difference in risk between the groups can be amplified if recent infection improves vaccine immunogenicity and vaccine-induced protection [29], as recently observed for SARS-CoV-2 [31].

In epidemiologic terms [32], under the infection block hypothesis, infection in the previous season is a mediator between vaccination in the previous season and a clinical infection outcome in the current season. When we estimate the effect of repeated vaccination, infection in the previous season, acting as a mediator, does not inherently introduce bias. However, if infection in the previous season influences the decision to vaccinate in the current season as well as the probability of clinical infection in the current season, then it is a confounder that can bias the estimated effect of repeated vaccination on clinical infection. Because infection in the previous season may be a mediator and a confounder, appropriately adjusting for it requires an approach that can handle this treatment-confounder feedback, such as inverse probability weighting [33].

In this study, we first assessed the effect of repeated vaccination after accounting for intraseason waning of vaccine protection. We then assessed whether documented clinical infection in the prior season, a potential confounder, may have biased our estimate of the effect of repeated vaccination. Finally, we theoretically assessed the plausibility of the infection block hypothesis and enhanced VE from recent subclinical and undocumented infections as explanations for the repeat vaccination effect.

METHODS

Study Setting and Population

During the study period, the US Flu Vaccine Effectiveness Network consisted of 5 study sites in Wisconsin, Michigan, Washington, Pennsylvania, and Texas [7, 10, 34–36] (Supplementary Section 1). The study was based on a test-negative design, estimating the odds of influenza infection in individuals who were vaccinated vs unvaccinated. During each enrollment season, outpatients aged ≥6 months were eligible for recruitment if they presented with acute respiratory illness with symptom onset within the last 7 or 10 days, depending on the Flu Vaccine Effectiveness Network site. Each eligible patient completed an enrollment interview that included questions on status of influenza vaccination in the study enrollment season (the current season), influenza vaccination in the immediately preceding season (the previous season), demographic information, and underlying health conditions. Participants were tested for influenza by real-time reverse transcription polymerase chain reaction (rRT-PCR) assay. Influenza-positive samples were first typed and then A-subtyped or B-lineage-typed. For simplicity throughout, we refer to individuals with medically attended, PCR-confirmed symptomatic influenza virus infection as having "clinical infection." Influenza vaccination status was confirmed by reviewing immunization records and state registries.

We analyzed data collected over 8 seasons (2011–2012 through 2018–2019) from all 5 sites. We excluded those who were vaccinated within 14 days of illness onset, for consistency with prior analyses. We also excluded anyone who received >1 dose each season before symptom onset and were <1 year of age at enrollment.

To study the impact of clinical infection history, we additionally obtained enrollment history and real-time reverse transcription PCR testing history from the Marshfield Clinic Health System (MCHS), the US Flu Vaccine Effectiveness Network site in Wisconsin. The analyses using exclusively MCHS data are described in the subsection titled "Adjustment for clinical infection history" of the Methods, and the results are shown in the subsection titled "Impact of Clinical Infection History" of the Results. The study design and the definition of clinical infection were consistent over time. As the primary outpatient and inpatient care provider in its catchment area, MCHS could collect data on enrollment and testing history that are not available from other sites [37]. In particular, participant data are linked across seasons. We analyzed data from the MCHS over 12 seasons (2007–2008 through 2018–2019). Eligible patients who were not approached or chose not to enroll were not included in the study. Therefore, we referred to 'documented' and 'undocumented' clinical infections in our analyses to emphasize that the study did not enroll all individuals who met the syndromic definition of influenza-like illness and would have tested positive in the prior season if they had been enrolled.

Statistical Analyses

Accounting for Within-Season Waning of Vaccine Protection

Using data from the 5 sites in the US Flu Vaccine Effectiveness Network, we first determined whether the timing of vaccination differed between repeat and nonrepeat vaccinees by fitting a linear regression model.

Using logistic regression models, we then estimated the relative odds of documented clinical infection among repeat vaccinees with reference to nonrepeat vaccinees after adjusting for time of vaccination in the current season (to account for the waning of vaccine protection; Supplementary Section 3). The study outcome is documented type/subtype-specific PCR-confirmed clinical infection. Independent variables are as follows: an indicator for having been vaccinated 2–9, 10–13, 14–17, 18–21, or >21 weeks before symptom onset in the current season regardless of prior-season vaccination status (with categorization consistent with Ray et al [19]); a dichotomous indicator for having been vaccinated only in the prior season; a dichotomous indicator for having been vaccinated in the current season and the prior season; and

age group, sex, comorbidity, influenza season, study site, and calendar month of symptom onset.

Adjustment for Clinical Infection History

Because MCHS was the only site that had linked participants' previous study enrollment and infection history, only data from MCHS could be used to assess the impact of clinical infection history.

To determine how a clinical infection in the current season is associated with documented clinical infection with the same and other types/subtypes in prior seasons, we assessed the odds ratio of clinical infection in the current season among individuals with no prior documented clinical infections or with documented clinical infections 3 to 5 or ≥6 seasons ago with reference to those whose last documented clinical infection was 1 or 2 seasons before the current season (Supplementary Section 4).

Using logistic regression models, we then assessed whether documented clinical infections in the previous season influenced the decision to vaccinate in the current season. The dependent variable was vaccination in the current season. The model was stratified by previous-season vaccination status and adjusted for age group, sex, comorbidity, and an indicator of vaccination frequency (Supplementary Section 4).

Next, we estimated the effect of repeated vaccination after adjusting for the documented clinical infection status of any type/subtype in the previous season (Supplementary Section 4). To handle the treatment-confounder feedback, we used inverse probability weighting to account for documented clinical infection status of any type/subtype in the previous season, using regression to adjust for baseline covariates. Weights were calculated as the inverse of each person's probability of being vaccinated in each season given one's previous vaccination status, documented clinical infection status in the prior season, and baseline covariates (ie, sex, age group, comorbidities, influenza season). These weights were then "stabilized" by using the probabilities of being vaccinated (given the vaccination history) and the aforementioned baseline covariates (excluding infection status in the prior season).

Impact of Subclinical and Undocumented Infection

To understand how history of subclinical or undocumented infection (ie, infections not detected by the US Flu Vaccine Effectiveness Network) may affect the estimated effect of repeated vaccination, we evaluated the proportion of repeat and nonrepeat vaccinees who would have had to have been subclinically infected or have had undocumented infection in the previous season to reproduce the estimated effect of repeated vaccination, assuming that the infection block hypothesis from subclinical or undocumented infection was the only explanation for the observed elevated risk. We demonstrate that the results are consistent with the hypothesis of enhanced vaccine immunogenicity postinfection.

To achieve this objective, we built a theoretical model and created a pseudo-population of repeat and nonrepeat vaccinees with various infection statuses in the previous seasons (Supplementary Section 5). We derived the relationship between rates of subclinical or undocumented infections in repeat and nonrepeat vaccinees given various degrees of effectiveness of subclinical or undocumented infection against future clinical infection (30%, 50%, and 70% reductions in clinical infection risk). We varied assumptions about the protection conferred by documented clinical, subclinical, or undocumented infection in the prior season against future infection. Based on estimates from prior studies [38, 39], we varied clinical attack rates in vaccinated and unvaccinated individuals, assuming either low clinical incidence (1% and 2% for vaccinated and unvaccinated, respectively) or high (3% and 6%).

The study obtained institutional review board approval at participating institutions and the Centers for Disease Control and Prevention.

RESULTS

Between the 2011–2012 and 2018–2019 seasons, participants enrolled in the US Flu Vaccine Effectiveness Network contributed 61 943 visits, of which 55 728 (90.0%) met the inclusion criteria of our analyses. Of those visits, 50.2% (27 986/55 728) were by individuals who had received 1 dose of the current seasonal influenza vaccine ≥14 days prior to the onset date of illness (Supplementary Figure 1.1). Among those vaccinated ≥14 days prior to illness onset, 73.7% (20 630/27 986) of visits were by participants who were vaccinated at least once in the previous season, whom we refer to as repeat vaccinees (Supplementary Table 1.1).

Impact of Waning Vaccine Protection

On average, repeat vaccinees of similar age, sex, and comorbidities were vaccinated 1.1 weeks (95% CI, 1.0–1.2) earlier than nonrepeat vaccinees (Figure 1*A*). Adjusting for the timing of vaccination in the current season did not notably change the marked repeat vaccination effect for A/H3N2 and had little to no effect for A/H1N1pdm09 and type B (Figure 1*B*; Supplementary Figure 3.3 shows variation in estimates by season and site; Supplementary Figure 3.5 shows that results did not vary significantly by age group).

In models accounting for the timing of vaccination and previous season vaccination, we observed that odds of documented clinical infection against all 3 types/subtypes increased with time since current season vaccination (Figure 1*C*). When compared with individuals not vaccinated in either season (who had the highest risk of testing positive), current-season vaccinees who vaccinated 2 to 9 weeks before testing had lower odds (odds ratio [OR], 0.29; 95% CI, .23–.35) for A/H1N1pdm09-associated illness than those vaccinated 18 to 21 weeks before

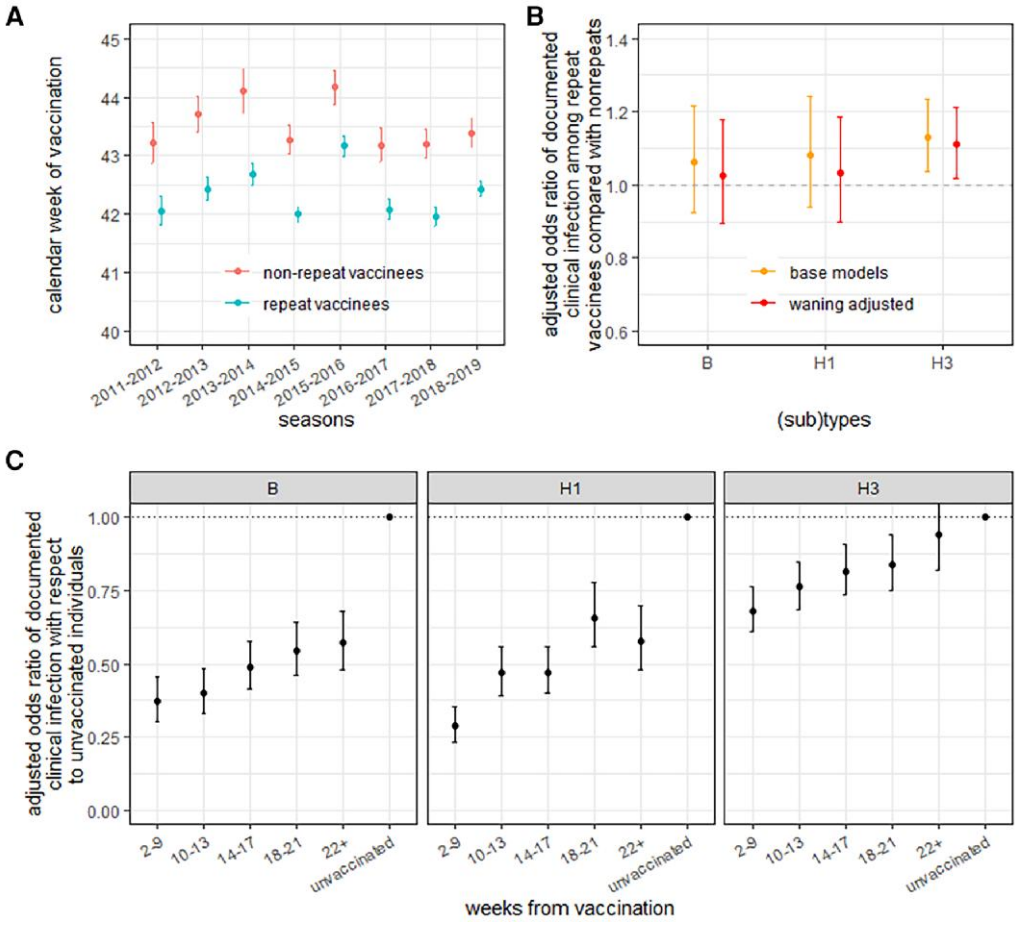

Figure 1. That repeat vaccinees vaccinate earlier in a season, which increases their susceptibility to infection due to waning vaccine protection, does not explain their higher odds of documented clinical infection as compared with nonrepeat vaccinees. *A*, Average calendar week of vaccination among repeat and nonrepeat vaccinees over the study enrollment seasons. Repeat vaccinees consistently get vaccinated earlier than nonrepeat vaccinees. *B*, Adjusted odds ratio for documented clinical infection among individuals vaccinated this season stratified by whether they were also vaccinated in the prior season or not (repeat or nonrepeat vaccinees), before (estimates using the "base models") and after (estimates using the "waning adjusted models") adjustment for the timing of vaccination within a season. Site- and season-specific data are shown in Supplementary Figure 3.3. *C*, Adjusted odds ratio of documented clinical infection comparing individuals vaccinated in the current season by weeks, but not in the previous season, before testing positive with respect to those not vaccinated in either season. Error bars indicate 95% CI. Site- and season-specific data are shown in Supplementary Figure 3.1, and age-specific data are shown in Supplementary Figure 3.5. See Supplementary Section 3 for detailed definitions of the quantities reported here.

testing (OR, 0.66; 95% CI, .56–.78). In the 2014–2015 season, when there was a mismatch between the A/H3N2 component and the circulating strains, the odds of documented clinical infection decreased with time from vaccination in Wisconsin (Supplementary Figure 3.1).

Impact of Documented Clinical Infection History

Prior documented clinical infections of the homologous type/subtype protected against clinical infections of type B or A/H3N2, with more recent documented infections conferring stronger protection (Figure 2*A*): those clinically infected with type B >6 seasons ago had 3.60 times (95% CI, 1.08–11.9) the odds of testing positive for type B in the current season than those who were clinically infected in the previous 1 or 2 seasons (Figure 2*A*). A similar trend emerged for documented clinical infections against A/H3N2 (OR, 32.4; 95% CI, 4.4–242; Figure 2*A*). We did not find documented clinical infections of a heterologous type/subtype to be protective (Supplementary Figure 4.1). Due to the limited number of A/H1N1pdm09 infections during our enrollment period, we could not assess the impact of homologous clinical infection with A/H1N1pdm09.

We found that having a documented clinical influenza virus infection in the previous season appeared to influence the decision to vaccinate in the current season. Individuals unvaccinated in the previous season were more likely to vaccinate in the current season (OR, 1.30; 95% CI, 1.18–1.44) if they had documented clinical infection in the previous season than if they had not. However, those who became infected after being vaccinated in the previous season were as

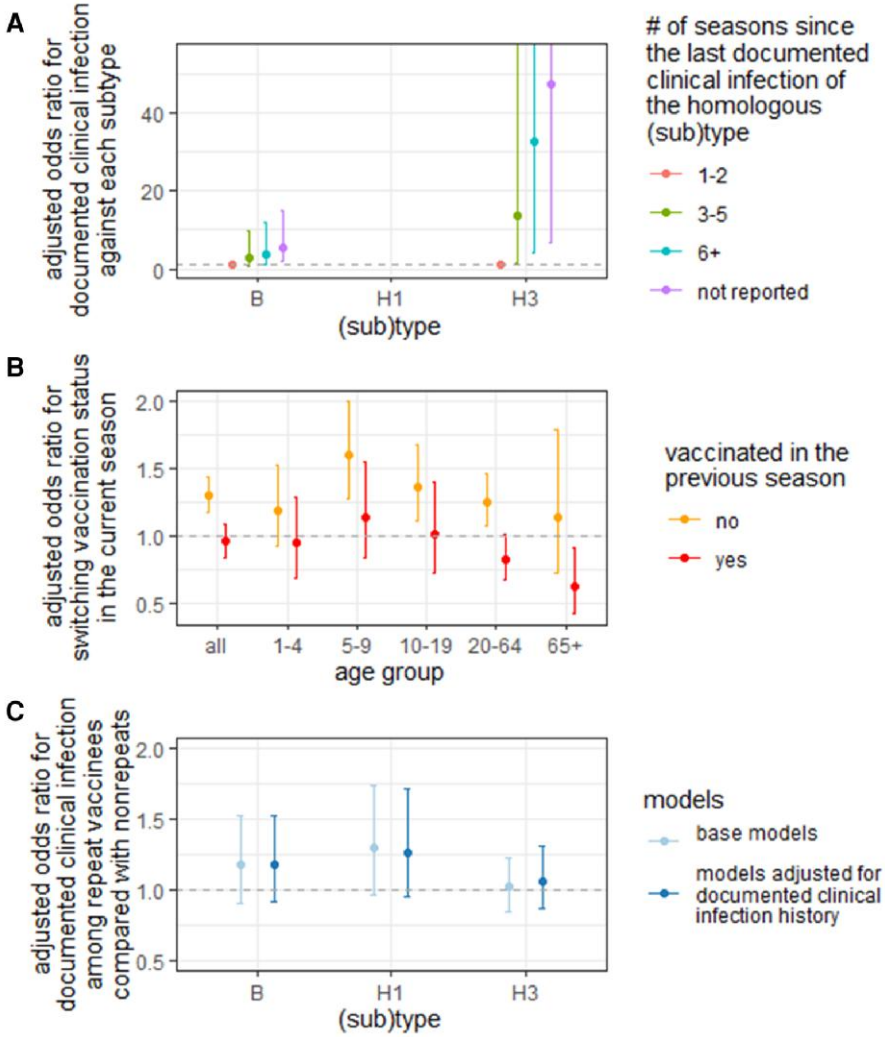

Figure 2. Recent documented clinical infections, which induce nonvaccinees to vaccinate the next season and which can protect against clinical reinfection for years, cannot explain the effect of repeated vaccination. *A*, Association between recent documented clinical infections and odds of clinical infection in the current influenza season. More distant documented clinical infections of the homologous subtype are associated with higher odds of current-season documented clinical infection. *B*, Tendency to switch vaccination status in the current influenza season after documented clinical infection in the previous season. When compared with individuals without confirmed infections, unvaccinated individuals who were clinically infected in the previous season were more likely to vaccinate in the current season. *C*, Estimated effect of repeat vaccination after adjusting for recent documented clinical infections. Adjusted odds ratio for clinical infection comparing repeat vaccinees with nonrepeat vaccinees before (estimates from the "base models") and after (estimates from the "models adjusted for documented clinical infection history") adjustment for documented clinical infection status in the previous season via inverse probability weighting. Results stratified by age group are shown in Supplementary Figure 4.4. They suggest a marginally higher adjusted odds of infection with statistical significance in repeat vaccinees >19 years old for H1N1. Adjustment did not significantly affect the estimates. Error bars indicate 95% CIs.

likely to be unvaccinated in the current season as those not infected (OR, 0.96; 95% CI, .85–1.10), with the exception of the oldest group, which tended to vaccinate again (Figure 2*B*).

Adjusting for confounding by documented clinical infection in the previous season had little influence on the estimated effect of repeated vaccination (Figure 2*C*). After adjustment, repeat vaccinees enrolled during the 2008–2009 season and between the 2010–2011 and 2018–2019 seasons had 1.29 times (95% CI, .96–1.71) the odds of testing positive for A/H1N1dpm09 than those who were vaccinated in only the current season. Accounting for documented clinical infection history did not significantly change the estimated effect of repeated vaccination against A/H3N2 (from 1.02 [95% CI, .84–1.23] to 1.06 [95% CI, .87–1.31] postadjustment) or type B (from 1.18 [95% CI, .91–1.53] to 1.17 [95% CI, .92–1.52] postadjustment). Excluding the 194 individuals who presented with acute respiratory illness but refused enrollment in the previous season did not significantly change the results (Supplementary Figure 4.2). Not adjusting for waning vaccine protection in the weighted outcome model yielded similar results (Supplementary Figure 4.3, Supplementary Section 4).

Impact of Documented and Undocumented Clinical and Subclinical Infection History

Infection Block Hypothesis

In the previous section, we estimated that repeat vaccinees had a 10% increase (approximate OR, 1.1) in the odds of current-season documented clinical infection, an effect that could be partially mediated by documented clinical infection in the prior season, a version of the infection block hypothesis. In this section, we use a theoretical model to explore the degree to which subclinical or undocumented infection—which would not be observed in any of the data sets that we consider—could fully explain the observed repeat vaccination effect.

To produce the estimated effect of repeated vaccination in the US Flu Vaccine Effectiveness Network (ie, for clinical infection comparing repeat with nonrepeat vaccinees against A/H3N2 or type B; OR, 1.1), nonrepeat vaccinees would have to be subclinically infected or have undocumented infection in the prior season at a substantially higher rate than repeat vaccinees (Figure 3, Supplementary Figure 5.1). For example, if subclinical or undocumented infection reduces the probability of next-season clinical infection by 70% (dark green curve in Figure 3*A*), approximately 5% of repeat vaccinees and approximately 15% of nonrepeat vaccinees would have to have been subclinically infected or have undocumented infection in the prior season to observe the estimated effect.

For thoroughness, we showed that prior-season documented clinical infection is unlikely to be an important mediator in this relationship between prior-season vaccination and the odds of current-season clinical infection (Supplementary Section 6, Supplementary Figure 6.1). When compared with estimates from a setting of low clinical incidence, in a high-incidence setting, we expect a greater excess of clinical infections in the current season among repeat vaccinees vs nonrepeat vaccinees (Supplementary Figure 5.2).

Enhanced Vaccine Immunogenicity Hypothesis

If recent infection improves vaccine immunogenicity and thus vaccine-induced protection, a smaller difference in rates of subclinical or undocumented infection between repeat and nonrepeat vaccinees would generate the same estimated effect of repeated vaccination against documented clinical infection in the current season (Supplementary Figure 5.3). For example, in the scenario described in the previous section, we would observe the expected effect of repeated vaccination (OR, 1.1)

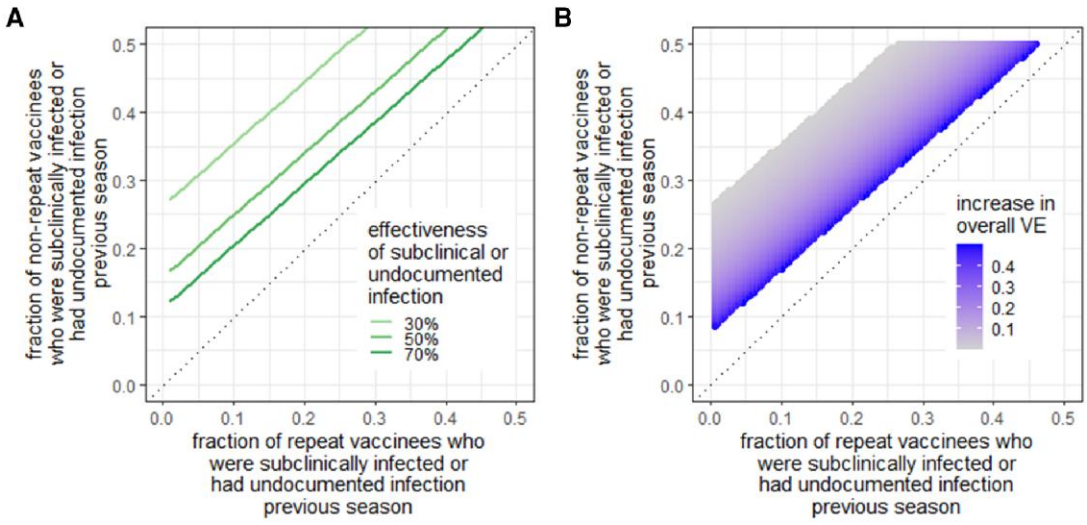

Figure 3. Subclinical or undocumented infection might be able to explain the effect of repeated vaccination, aligning with the hypotheses of (*A*) infection block and (*B*) enhanced immunogenicity. *A*, The fraction of repeat and nonrepeat vaccinees who would need to have been subclinically infected or have undocumented infection in the previous season to reproduce the estimated effect of repeated vaccination in the US Flu Vaccine Effectiveness Network (ie, OR, 1.1), given various assumptions of predetermined protection against clinical infection after subclinical or undocumented infection (30%, 50%, 70%). See Supplementary Section 5 for detailed methods. Under this hypothesis, subclinical or undocumented infection is more common among those unvaccinated in the previous season (green lines above the 45° line) and reduces risk of infection this season. Only the plausible range of attack rate of subclinical and undocumented infection among repeat vaccinees (x-axis) and nonrepeat vaccinees (y-axis; 0%–50%) are shown in the figure. *B*, The absolute increase in vaccine effectiveness from a baseline of 50% needed to reproduce the estimated effect of repeated vaccination in the US Flu Vaccine Effectiveness Network (OR, 1.1). Under this hypothesis, vaccination this season is more effective in those infected subclinically or with undocumented infection in the previous season, who are (as in panel *A*) more common among those unvaccinated in the previous season. The figure shows the scenario where the effectiveness of subclinical or undocumented infection against future clinical infection is 30%. The uncolored portion of the figure represents the population where a boost in vaccine effectiveness after infection will not generate the estimated effect of repeated vaccination (OR, 1.1). The results in both panels assume that vaccine effectiveness against clinical infection is 50%; the clinical attack rate among vaccinees in a season is 1%; the current-season clinical attack rate among the subset of current-season vaccinees not infected in the previous season is 1.5%; and documented clinical infection in the previous season perfectly protects against clinical infection in the following season.

when the difference in the rate of subclinical or documented infection between repeat and nonrepeat vaccinees is 10% (eg, approximately 5% and 15%, respectively), assuming that subclinical or undocumented infection reduces the probability of future clinical infection by 70%. But if recent infection boosts VE from 50% to 76%, a smaller difference in attack rate from subclinical or undocumented infection (approximately 5% in repeat vaccinees and 12% in nonrepeat vaccinees) and weaker protection from subclinical or undocumented infection (from 70% to 30%) can produce the same estimated effect.

DISCUSSION

Observational studies [7–13, 15, 16], mostly based on the test-negative design [8–13, 15, 16], have provided critical information on influenza VE. These studies can have biases and uncontrolled confounding that affect inference, including inference of VE in different subpopulations [34, 40–43]. Reduced VE in repeat vaccinees has been a troubling, intermittent, and largely unexplained phenomenon [8, 9]. We studied a component phenomenon, which is that the absolute risk (or odds) of infection among vaccinees in the current season is less if they were unvaccinated last season than if they were vaccinated last season. We observed waning of vaccine protection and repeat vaccinees' tendency to vaccinate earlier within a season as compared with nonrepeat vaccinees. We showed that clinical infection affects one's decision to vaccinate in the next season and that documented clinical infections in the past 1 or 2 seasons strongly protect against reinfection. However, these potentially biasing factors—prior-season clinical infection and timing of vaccination—could not fully explain the higher risk of clinical infection in the repeat vs nonrepeat vaccinees in our study population. We showed that the residual repeat vaccination effect might be explained by different rates of subclinical infection or undocumented infection between repeat and nonrepeat vaccinees via 2 proposed mechanisms: the infection block hypothesis [4, 25–27] and enhanced vaccine immunogenicity and protection postinfection [29, 44]. The difference in rates of subclinical or undocumented infection between the groups and its variation from one season to the next might thus underlie variability in estimated effects of repeated vaccination.

Mostly due to lack of data, clinical infection history has typically not been accounted for when estimating influenza VE. We found that accounting for documented clinical infection history did not substantially change the estimated effect of repeat vaccination, indicating that confounding by prior-season documented clinical infection may not fully explain the elevated odds of infection among repeat vaccinees. Aside from a potential role as a confounder, we found documented clinical infection unlikely to act as an important mediator. Verifying the finding in surveillance data requires methods that can tease apart the direct and indirect effects of vaccination after taking into account the interaction of vaccination and infection over a multiyear period.

The sensitivity of the estimated effect of repeated vaccination to differences in subclinical attack rates and infection-associated protection suggests a possible explanation for the observed variability in the estimated effect of repeat vaccination and other VE measures across locations and time. There is well-known spatiotemporal variation in the sizes of influenza epidemics and in circulating clades that could affect the amount of protection conferred by infection in different populations. Our results suggest a need to try to account more precisely for past infections so that VE estimates can be compared across populations stratified by similar infection history. Longitudinal cohort studies that involve blood collection, active surveillance, and sequencing can be useful for identifying subclinical infections, and coupling these observations with health care–seeking behavior and PCR testing can help test the infection block and enhanced immunogenicity hypotheses [45]. Eventually, stratification on infection history may be possible through surrogate immune markers.

The study has several limitations. Throughout our analysis, we assumed that influenza vaccination with any type of influenza vaccine confers complete protection in a subset of vaccinees. We did not consider "leaky" vaccine effects, where vaccines are partially protective in all recipients, which can lead to an observed decline in VE estimates even when vaccine protection does not wane [46]. Although the test-negative study, by selecting only patients who seek medical care, is designed to reduce the difference in health-seeking behavior between cases and noncases, it does not eliminate it [41]. In the study of prior clinical infection history using the data from Marshfield, only a fraction of all individuals presenting for care with influenza-like illness participated each season. Therefore, those with documented clinical infection in a prior season represent a fraction of all individuals who met the syndromic definition of influenza-like illness and would have tested positive in the prior season if they had enrolled in the prior season. We did not explore birth cohort effects or the effects of antigenic distance on protection [47–50]. Since we assumed that people without enrollment records in the previous season were not clinically infected, some of them may have been misclassified.

The practical benefits of annual vaccination programs should not be extrapolated from this analysis of the relative risk of infection in repeat vaccinees vs nonrepeat vaccinees. The choice between an annual and nonannual vaccination program should be based on assessments of the infection risk among all repeat and nonrepeat vaccinees as well as those who are unvaccinated. Our analysis does not compare the risk of infection between repeat vaccinees and those vaccinated in the prior season only, who would be part of a hypothetical nonannual vaccination program.

Our study provides evidence that 2 potential factors—timing of vaccination and documented clinical infection history—

cannot fully explain the increased infection risk in repeat vaccinees as compared with nonrepeat vaccinees. Documented clinical infection history is further unlikely to act as a strong mediator to explain the repeated vaccination effect. Instead, under reasonable assumptions, the infection block and enhanced immunogenicity hypotheses involving subclinical or undocumented infection in the previous season may explain the effect, thus acting as a potential mediator. Estimation of VE requires careful consideration of time since vaccination and infection history of different subpopulations.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Author contributions. Q. B., B. A. D., M. L., and S. C. conceived of the study. H. Q. N., E. T. M., M. G., K. J. W., G. K. B., and B. F. collected the data. Q. B. performed the analyses and generated all figures. Q. B., B. A. D., M. L., and S. C. wrote the manuscript. All authors revised the manuscript.

Data availability. Data and relevant code are available at https://github.com/cobeylab/FluVE_repeatvac_public. The analyses were conducted in R version 4.1.1.

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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