Effects of Sequential Influenza A(H1N1)pdm09 Vaccination on Antibody Waning

Jon Zelner,^{1,2,a} Joshua G. Petrie,^{1,a,*} Rob Trangucci,³ Emily T. Martin,¹ and Arnold S. Monto¹

¹Department of Epidemiology, and ²Center for Social Epidemiology and Population Health, University of Michigan School of Public Health, and ³Department of Statistics, University of Michigan, Ann Arbor

Background. Antibody waning following influenza vaccination has been repeatedly evaluated, but waning has rarely been studied in the context of longitudinal vaccination history.

Methods. We developed a Bayesian hierarchical model to assess the effects of sequential influenza A(H1N1)pdm09 vaccination on hemagglutination inhibition antibody boosting and waning in a longitudinal cohort of older children and adults from 2011 to 2016, a period during which the A(H1N1)pdm09 vaccine strain did not change.

Results. Antibody measurements from 2057 serum specimens longitudinally collected from 388 individuals were included. Average postvaccination antibody titers were similar across successive vaccinations, but the rate of antibody waning increased with each vaccination. The antibody half-life was estimated to decrease from 32 months (95% credible interval [CrI], 22–61 months) following first vaccination to 9 months (95% CrI, 7–15 months) following a seventh vaccination.

Conclusions. Although the rate of antibody waning increased with successive vaccination, the estimated antibody half-life was longer than a typical influenza season even among the most highly vaccinated. This supports current recommendations for vaccination at the earliest opportunity. Patterns of boosting and waning might be different with the influenza A(H3N2) subtype, which evolves more rapidly and has been most associated with reduced effectiveness following repeat vaccination.

Keywords. influenza; influenza vaccine; antibody; waning; hemagglutinin.

Influenza infections result in substantial morbidity and mortality each year [1, 2]. In the United States, all persons >6 months of age are recommended to receive influenza vaccine annually to reduce the risk of infection [3]. However, in many recent years, vaccine effectiveness (VE) has been lower than expected and reduced VE has been observed with repeated vaccination in some years [4]. Because circulating influenza viruses are constantly evolving, the strains included in the vaccine are evaluated on an annual basis [5]. If the viruses that are expected to circulate are determined to have sufficient antigenic differences in the hemagglutinin surface protein relative to those included in the past season's vaccine, then the corresponding strains for the next season's vaccine will be updated. Conversely, the same strain may be included in the vaccine over multiple seasons if antigenic changes are not detected. Therefore, individuals may have repeated exposure to related, or identical, influenza antigens through vaccination and infection over time. The overall effect of this repeated exposure on subsequent vaccine response

and protection from infection remains an unresolved question. However, it has been hypothesized that reduced VE with repeat vaccination is more likely to occur when there is a smaller antigenic distance between the virus in the prior and subsequent years' vaccines [6].

Antibody against influenza virus hemagglutinin is a well-established correlate of protection against influenza infection [7]. Quantities of these antibodies are dynamic, increasing in the weeks following influenza infection or vaccination and then waning over time. Reduced antibody response following vaccination has been demonstrated among those vaccinated in consecutive years compared to those vaccinated for the first time [8–11]. However, the longer-term boosting and waning dynamics of antibody following annual vaccination have not been extensively studied. These dynamics have clear implications for vaccine-induced protection from influenza infection, given recommendations for annual vaccination.

The influenza A/California/07/2009 (H1N1)pdm09 strain was included in influenza vaccines beginning with the monovalent vaccine used during the 2009 pandemic and continuing as a component of seasonal influenza vaccines from 2010 through 2017 [12]. The consistent inclusion of this influenza strain in vaccines presents a unique opportunity to study antibody response to a single antigen over multiple years. The Household Influenza Vaccine Evaluation (HIVE) Study has been ongoing since 2010 with serologic specimens for immunologic studies

Received 12 October 2018; editorial decision 25 January 2019; accepted 30 January 2019; published online February 4, 2019.

^aJ. Z and J. G. P. contributed equally to this work.

Correspondence: J. G. Petrie, PhD, University of Michigan School of Public Health, 1415 Washington Heights, Ann Arbor MI 48109 (jpetrie@umich.edu).

The Journal of Infectious Diseases® 2019;220:12–9

© The Author(s) 2019. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com. DOI: 10.1093/infdis/jiz055

of vaccine response and subsequent susceptibility to infection collected since 2011 in a population with high levels of vaccine uptake [13]. We investigated the kinetics of antibody to influenza A/California/07/2009 (H1N1)pdm09 among HIVE study participants over 5 influenza seasons and compared patterns of antibody boosting and waning following vaccination by prior vaccination history.

METHODS

Study Population

The HIVE study is a prospective cohort of households with children living in Ann Arbor, Michigan, and the surrounding area. Recruitment into the cohort occurred annually during the study years included in this analysis. Although households committed to only 1 year of participation at a time, participation for multiple seasons was encouraged. In this analysis, we focused on individuals who participated in the 2015–2016 study year and included all available data from past seasons.

Households were identified, recruited, and enrolled from May through August 2015 prior to the 2015–2016 influenza season, as previously described [14]. All households also participated in the 2014–2015 study year, and a subset participated for multiple previous seasons going back to the 2010–2011 study year. In each year of participation, households completed an enrollment interview and were followed prospectively for identification of acute respiratory illnesses; ill household members had combined throat and nasal specimens collected by research staff, which were tested for influenza by reverse-transcription polymerase chain reaction (RT-PCR) [14]. Annual influenza vaccination, including prior vaccination history, was documented by electronic medical records and the state of Michigan's vaccination registry. Beginning in the fall of 2011, blood was collected twice annually (fall and spring) from participants ≥ 13 years of age. Fall specimens represent pre-influenza season and postvaccination timing for individuals who chose to be vaccinated. Spring specimens represent postseason timing for the immediately prior influenza season and prevaccination timing for the following season. In all study years, adult household members provided informed consent for themselves and their children. The study was approved by the University of Michigan Medical School Institutional Review Board.

Serum specimens were tested in hemagglutination inhibition assays (HAIs) using monovalent inactivated influenza vaccine subunit material (Sanofi Pasteur) representing the A/California/7/2009 (H1N1)pdm09 virus present in the monovalent 2009 pandemic vaccine and all seasonal influenza vaccines from 2010 through 2016. A ≥ 4 -fold rise in influenza A(H1N1)pdm09 HAI antibody titer between paired serum specimens bracketing any influenza season was also used to identify influenza A(H1N1)pdm09 infections in addition to RT-PCR.

Models

Analyses were restricted to individuals who received at least 1 influenza vaccination since 2009. Individuals with influenza A(H1N1)pdm09 infection confirmed by RT-PCR or serology were censored at the time of their last blood collection prior to infection.

Following Petrie et al [15], we modeled antibody waning as a process of exponential decay of the individual's $\log_2$ HAI titer. Waning was assumed to begin 4 weeks after vaccination, to account for the period between vaccination and peak titer [11, 16]. We extended this original model by allowing the rate of antibody boosting and waning to vary across (1) individuals, indexed by i ; and (2) successive H1N1 vaccinations, indexed by j . We differentiated between an individual's *unobserved* continuous titer value, denoted y_{ij}^* , and their *observed* discrete titer value, denoted y_{ij} . We modeled variation in the observed value of y_{ij} owing to stochastic variation in the HAI assay using an ordered logit model [17]. We used a hierarchical Bayesian framework to account for variation in rates of titer boosting and waning across individuals, i , and by total vaccines received, j . We denoted individual i 's monthly rate of decay in the value of y_{ij}^* by the parameter γ_{ij} .

Because serum specimens were obtained at irregular time intervals relative to vaccination, the values y_{ij}^* in the weeks following vaccination, representing the intensity of boosting, cannot be observed directly and need to be estimated. In our model, the magnitude of boosting is represented by an intercept term, α_{ij} , that includes the population mean titer value following vaccination j ($\bar{\alpha}_j$); individual covariates influencing the rate of boosting, such as age, sex, and influenza season (represented by coefficients β); and unobserved individual-level heterogeneity denoted by the zero-mean individual random effects ϵ_i^α . So, the value of an individual's titer after vaccination j can be written as:

$$\log(\alpha_{ij}) = \log(\bar{\alpha}_j) + X_{ij}\beta + \epsilon_i^\alpha$$

Similarly, an individual's rate of titer waning following vaccination j can be written as a combination of the population mean rate of waning following vaccination j , denoted $\bar{\gamma}_j$, and a zero-mean random effects representing within-individual heterogeneity in the rate of postvaccination waning, ϵ_i^γ :

$$\log(\gamma_{ij}) = \log(\bar{\gamma}_j) + \epsilon_i^\gamma$$

We denoted the month individual i received vaccination j as Ω_{ij} . We combined this value with the terms γ_{ij} and α_{ij} to predict the individual's titer value at any time after vaccination j and before vaccination $j + 1$, i.e., ($\Omega_{ij} < t < \Omega_{i,j+1}$) as follows:

$$y_{ij}^*(t) = \alpha_{ij}e^{-\gamma_{ij}(t-\Omega_{ij})}$$

Because the individual's HAI titer is only observed at discrete serial dilution intervals, (1/10, 1/20, ...), we used a Bayesian

hierarchical ordered logistic regression model to represent observation error in the translation from continuous unobserved HAI threshold values to discrete titer observations. A 1-unit change in exponentiated coefficients from this model can be interpreted as multiplying the baseline titer by the specified amount. We refer to these as titer ratios (TRs). To account for potential nonlinearity in the effect of age and birth cohort, these factors were modeled using a flexible Gaussian process smoother. For a complete description of this model, see Section 1 in the Supplementary Materials.

Sensitivity Analyses

To assess whether results were robust across models, waning rates were also estimated in linear mixed models with log₂ titers as the dependent variable, and time in days from the date of most recent vaccination as the independent variable; age, sex, influenza season, the number of cumulative vaccinations, and a time by cumulative vaccine interaction term were also included in the model. To account for correlation of titers within individuals over time, the intercept and time were modeled as random effects. Antibody titer half-lives were calculated as the reciprocal of the estimated rate of antibody decline per month and compared for each model.

RESULTS

Population Characteristics

Overall, 464 individuals from 222 households participated and provided at least 1 serum specimen in the 2015–2016 study year. Most individuals (99%) participated for >1 year, 60% participated for ≥4 years, and 31% participated in all 6 years. Nineteen percent of participants were <18 years of age in 2015–2016, 59% were female, and 76% were white. We obtained history of

receipt of all influenza A(H1N1)pdm09-containing vaccines from 2009–2010 through 2015–2016; 25% of participants were vaccinated in each of these 7 seasons and 16% were not vaccinated in any season. Table 1 shows the demographics of the 388 participants who received 1 or more vaccinations. The number of influenza seasons vaccinated did not vary by participant characteristics. A total of 57 influenza A(H1N1)pdm09 infections were identified by RT-PCR or serology in 53 individuals, primarily in the 2013–2014 and 2015–2016 influenza seasons.

A total of 2790 blood specimens were collected from participants in the spring and fall of each year from 2 December 2011 through 8 September 2016; each specimen contributed an observation to the data. Observations of individuals with laboratory-confirmed influenza A(H1N1)pdm09 infection were censored at the time of their last blood collection prior to infection. This resulted in exclusion of 205 observations. An additional 528 observations were excluded from 114 individuals who had no postvaccination titer observations during the study period. This included the 76 individuals with no vaccinations, and an additional 38 individuals who were infected prior to their first vaccination. This resulted in HAI antibody measurements from a total of 2057 serum specimens being included in the analysis. Supplementary Table 1 shows the number of serum specimens collected by influenza season and total number of vaccinations received.

Impact of Serial Vaccination on Magnitude of Titer Boosting and Waning Rate

We modeled the boosting, and subsequent waning, of HAI antibody titer following repeated vaccination over time in models adjusted for birth year and study year. The average estimated peak postvaccination HAI titer did not significantly vary by number of previous vaccinations. This suggests that, at the

Table 1. Characteristics of Participating Household Members by Number of Influenza Seasons Vaccinated (2009–2010 to 2015–2016)—Household Influenza Vaccine Evaluation Study, Ann Arbor, Michigan

Characteristic	All Subjects	Vaccinated 1–2 Seasons	Vaccinated 3–4 Seasons	Vaccinated 5–6 Seasons	Vaccinated 7 Seasons
Age category					
13–17 y	71 (18.3)	8 (12.1)	9 (12.3)	30 (22.6)	24 (20.7)
18–49 y	276 (71.1)	51 (77.3)	59 (80.8)	91 (68.4)	75 (64.7)
≥50 y	41 (10.6)	7 (10.6)	5 (6.9)	12 (9.0)	17 (14.7)
Sex					
Male	164 (42.3)	32 (48.5)	33 (45.2)	52 (39.1)	47 (40.5)
Female	224 (57.7)	34 (51.5)	40 (54.8)	81 (60.9)	69 (59.5)
Race					
White	295 (76.0)	46 (69.7)	58 (79.5)	108 (81.2)	83 (71.6)
Black	28 (7.2)	9 (13.6)	3 (4.1)	9 (6.8)	7 (6.0)
Asian	32 (8.3)	6 (9.1)	6 (8.2)	7 (5.3)	13 (11.2)
Other/unknown	33 (8.5)	5 (7.6)	6 (8.2)	9 (6.8)	13 (11.2)
High-risk health condition					
Any	115 (29.6)	20 (30.3)	23 (31.5)	39 (29.3)	33 (28.4)
None	273 (70.4)	46 (69.7)	50 (68.5)	94 (70.7)	83 (71.6)
Total	388 (100.0)	66 (17.0)	73 (18.8)	133 (34.3)	116 (29.9)

Data are presented as No. (%).

population level, repeat vaccination was not associated with reduced postvaccination titers against influenza A(H1N1) pdm09. For example, a 42-year-old individual, corresponding to the median age of the cohort in 2016, had an average postboosting titer of 107.8 (95% credible interval [CrI], 70.9–159.2) after their first vaccination, and 96.5 (95% CrI, 53.8–164.2) after their seventh vaccination.

Although we did not observe a relationship between the cumulative number of vaccinations and magnitude of HAI antibody boosting, the rate of antibody waning increased with number of vaccinations (Figure 1 and Supplementary Figure 1). The rate of HAI titer waning was estimated to increase monotonically from 2.2% (95% CrI, 1.1%–3.2%) per month following an individual's first vaccination to 7.3% (95% CrI, 4.5%–9.7%) per month following their seventh vaccination (Supplementary Figure 2). This implies that a 2-fold decrease in HAI titer would take 32 months (95% CrI, 22–61 months) following an individual's first vaccination and 9 months (95% CrI, 7–15 months) following the seventh vaccination. Uncertainty in the value of $\bar{\gamma}_j$ also increased with the total number of vaccinations as evidenced by increasing 95% CrI breadth (Figure 1). This is likely due to the decreasing number of individuals with each successive level of vaccination, as well as fewer observations per individual, owing to the fact that by definition there are fewer years to observe postvaccination with each succeeding vaccination

event. To validate our Bayesian hierarchical model, we compared it to the linear mixed-effects model typically used in antibody waning analyses, for example, [15], and found that both models generated similar estimates (Supplementary Table 2).

Because the models were adjusted for both birth year and the study year each HAI observation was obtained, we were able to assess age, period, and cohort factors on average HAI titers. On average, individuals born after 1995 had higher HAI titers at any given time (Figure 2), with the largest effect among individuals born in 2000 (TR, 3.3 [95% CrI, 1.9–7.7]). After adjustment for birth cohort, there was no residual relationship between age and average HAI titer (Supplementary Figure 3). However, it is difficult to disentangle some age/cohort effects from overall vaccination effects. For example, if younger individuals are more likely to receive a greater number of vaccinations, this may be reflected in a higher average titer for younger cohorts, even after adjustment for effects of serial vaccination. However, our use of a flexible Gaussian process smoother to model age and birth cohort effects in each year should mitigate this risk. There was some suggestion of increasing titers by study year; however, only the 2013–2014 season had significantly higher titers relative to the 2011–2012 season (Supplementary Figure 4). This pattern, along with the statistically significant increase in titers in the 2013–2014 season in which influenza A(H1N1)pdm09 viruses predominated, might suggest the presence of undetected

Figure 1. Predicted postvaccination titer (upper panel) and monthly percentage decline in hemagglutination inhibition (HAI) titer (lower panel) by number of vaccinations for an individual aged 42 years, corresponding to the median age in the cohort data, in 2009. Error bars indicate 95% posterior credible interval; dots indicate posterior median.

Figure 2. Relative change in baseline hemagglutination inhibition titer as a function of birth cohort. Vertical bars indicate age-specific 95% posterior credible intervals.

infections that we were unable to exclude. However, the fact that the posterior credible intervals for all seasons other than 2013–2014 include zero suggest that any residual seasonal variation is captured by the modeled covariates and individual-level random effects. We also adjusted for sex (female TR, 1.09 [95% CrI, .88–1.34]) and number of influenza seasons between successive vaccinations (TR, 0.96 [95% CrI, .86–1.07]), but found that neither was associated with average HAI titer.

In addition to allowing variation in rates of boosting and waning across vaccinations, our model also accounts for

individual-level variation in these quantities. Our results indicate that there is considerable between-individual variation in boosting, even after covariate adjustment, with a standard deviation of $\hat{\sigma}_{\alpha} = 0.87$ (95% CrI, .79–.97). By contrast, we estimated minimal variation in the rate of antibody waning across individuals: $\hat{\sigma}_{\gamma} = 9.4 \times 10^{-4}$ (95% CrI, 5.3×10^{-5} – 2.7×10^{-3}).

Posterior Simulation of Impact of Serial Vaccination on HAI Titer Trajectory

Figure 3 shows the posterior predictive distribution of the trajectory of observed HAI titer within an individual, with birth year

Figure 3. Marginal posterior predictive distribution of hemagglutination inhibition titer evolution within an individual aged 42 years at first vaccination, over 7 annual vaccinations. Each line shows the proportion of simulations in which the simulated individual had a titer value greater than or equal to the specified titer value. The horizontal dashed line indicates threshold where $\leq 50\%$ of individuals have observed hemagglutination inhibition titer greater than or equal to the specified value.

and study year covariates fixed at median values and without individual-specific random effects, who has received 7 annual influenza A(H1N1)pdm09-containing vaccinations. The lines in the plot represent the proportion of individuals with titer greater than or equal to the specified titer by time since first vaccination. These trajectories visually demonstrate our earlier findings that the estimated peak postvaccination titer did not vary with successive vaccination, but that the rate of subsequent waning did increase with each annual vaccination.

DISCUSSION

Reduced VE among those vaccinated in consecutive years has been documented in several recent influenza seasons [4]. Prior to these observations of lower VE, reduced antibody response following repeated vaccination had also been demonstrated [8–11]. The effects of sequential vaccination on the persistence of vaccine-induced antibody have not been as extensively studied, but it is clear that both antibody boosting and waning dynamics play a role in determining an individual's level of protection from infection. In the current study, we found that population average postvaccination antibody titers against influenza A(H1N1)pdm09 were similar across successive vaccinations, but that the rate of antibody waning increased with increasing vaccination, from a half-life of 32 months following a first vaccination to 9 months following a seventh vaccination. A recent 5-year study of influenza A(H1N1)pdm09 antibody boosting and waning in Norwegian healthcare workers similarly found no difference in antibody boosting comparing those vaccinated every year to those occasionally vaccinated. However, in contrast to our findings, there was no indication of more rapid waning among those more frequently vaccinated [18].

We previously demonstrated that the short-term rate of antibody waning is faster among individuals with higher postvaccination antibody titers [15]. It might be expected that those who have received more previous vaccine doses might have higher antibody titers at any given time, and that this might account for our finding. However, in the current study, we found that the average magnitude of postvaccination antibody titers was consistent across successive vaccinations, but that the rate of titer waning accelerated with total vaccinations. A key distinction between the current analysis and our earlier one is that the data in [15] came from a clinical trial in which all participants had titer observations at multiple, equally spaced time points over an 18-month period postvaccination. In the longer-term study presented here, most individuals had 1 or 2 serum samples collected per season, making it difficult to directly measure small changes in the rate of within-season waning between individuals.

One potential biological mechanism to explain the faster average rate of postvaccination waning with repeated vaccination could be that first vaccinations might induce a large antibody

response that is broadly cross-reactive to multiple virus hemagglutinin epitopes [19, 20]. In contrast, subsequent vaccination might induce a smaller, but more targeted antibody response that is more efficient at neutralizing the virus. In this scenario, postvaccination HAI titers may appear to be similar for those with and without extensive vaccination history because the assays only measure overall inhibition of hemagglutination rather than epitope-specific binding [21]. However, waning could appear faster in those with multiple prior vaccinations because their overall pool of antibody is smaller. Studies have demonstrated that the antibody response to influenza vaccination is not homogenous with varying specificity to different epitopes of the influenza hemagglutinin, supporting this hypothesis [19]. It has also been demonstrated that repeated exposure to antigenically related viruses selects for antibodies that are narrowly focused in their recognition of viral epitopes [19, 20, 22–24].

When assay target antigens are well matched to the influenza viruses that circulate, HAI antibody titer is a strong correlate of protection [7]. Therefore, waning antibody titer can lead to increased risk of infection if the time between vaccination and influenza exposure is long. In the United States, most influenza vaccination typically occurs between September and November each year; however, the vaccine may be available as early as July in some locations. Influenza activity typically peaks between December and February each year, but circulation can continue into the late spring [25]. This can result in long periods of time between vaccination and potential exposure, which could result in reduced protection. It is currently recommended that individuals receive vaccination at the earliest opportunity [3]. Given that the shortest half-life estimated in this study was 9 months, this strategy is likely still the best option, considering the risk of missed opportunities for vaccination and the potential for early infections. This is also consistent with studies that have directly estimated relatively modest waning of VE [26, 27].

The influenza A(H1N1)pdm09 vaccine strain remained unchanged throughout the 5-year study period reported here. This presented a unique opportunity to study antibody dynamics in the context of repeated exposure to identical antigens. However, it should be noted that circulating A(H1N1)pdm09 did undergo antigenic drift during this time, and vaccine-specific antibody titer may not be an accurate measure of protection for all individuals [23,28]. Influenza A(H3N2) viruses evolve more quickly, leading to more frequent updates to the vaccine strain [29]. Given that influenza A(H3N2) is typically associated with larger seasonal outbreaks and more severe disease [2, 30, 31], and VE against influenza A(H3N2) has been low [32], it is a priority to determine how antibody develops and persists after repeated exposure to vaccination and infection. Unfortunately, accounting for additional unique circulating and vaccine strain antigens complicates modeling of the dynamics of influenza

A(H3N2) antibody. This model provides an important first step toward understanding the more complicated dynamics of influenza A(H3N2)-directed antibody. Extending the model to understand the dynamics of influenza B antibody might be an intermediate step given that the virus has been more stable than influenza A(H3N2), but there have been more vaccine strain changes than for A(H1N1)pdm09.

The National Institute of Allergy and Infectious Diseases recently published a strategic plan for development of a universal influenza vaccine [33]. In the context of this plan, the desired characteristics of a universal vaccine are that it provide broad protection against influenza A viruses that lasts for at least 1 year. It is conceivable that a vaccine might be developed that requires annual administration of an unchanging influenza antigen that induces broad immunity targeting less variable viral proteins. The results of this study suggest that accelerated waning protection could become an issue with other repeatedly administered influenza vaccines. Increasing the duration of vaccine-induced immunity should be prioritized along with increasing the breadth of immunity.

The results presented here represent a first step toward the development of models that can be used to develop optimized vaccination schedules that account for long-term antibody dynamics. Ideally, such models will also account for the impact of natural infection on the magnitude of titer boosting and waning over time. Development of these analytic tools that can be paired with longitudinal cohort studies of the development of influenza immunity could inform the development of the next generation of influenza vaccines and the policy decisions regarding their optimal use.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases online*. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Financial support. This work was supported by the Centers for Disease Control and Prevention (grant number U01 IP000474); the National Institute of Allergy and Infectious Diseases (NIAID) (grant number R01 AI097150); and an NIAID-funded Center of Excellence for Influenza Research and Surveillance (contract number HHSN272201400006C).

Potential conflicts of interest. E. T. M. has received grant support from Merck and consultancy fees from Pfizer. A. S. M. has received consultancy fees from Sanofi Pasteur and Seqirus. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Reed C, Chaves SS, Daily Kirley P, et al. Estimating influenza disease burden from population-based surveillance data in the United States. *PLoS One* **2015**; 10:e0118369.
2. Rolfes MA, Foppa IM, Garg S, et al. Annual estimates of the burden of seasonal influenza in the United States: a tool for strengthening influenza surveillance and preparedness. *Influenza Other Respir Viruses* **2018**; 12:132–7.
3. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2017–18 influenza season. *Am J Transplant* **2017**; 17:2970–82.
4. Belongia EA, Skowronski DM, McLean HQ, Chambers C, Sundaram ME, Serres GD. Repeated annual influenza vaccination and vaccine effectiveness: review of evidence. *Expert Rev Vaccines* **2017**; 16:723–36.
5. Carrat F, Flahault A. Influenza vaccine: the challenge of antigenic drift. *Vaccine* **2007**; 25:6852–62.
6. Smith DJ, Forrest S, Ackley DH, Perelson AS. Variable efficacy of repeated annual influenza vaccination. *Proc Natl Acad Sci USA* **1999**; 96:14001–6.
7. Ohmit SE, Petrie JG, Cross RT, Johnson E, Monto AS. Influenza hemagglutination-inhibition antibody titer as a correlate of vaccine-induced protection. *J Infect Dis* **2011**; 204:1879–85.
8. Sasaki S, He XS, Holmes TH, et al. Influence of prior influenza vaccination on antibody and B-cell responses. *PLoS One* **2008**; 3:e2975.
9. Beyer WE, Palache AM, Sprenger MJ, et al. Effects of repeated annual influenza vaccination on vaccine sero-response in young and elderly adults. *Vaccine* **1996**; 14:1331–9.
10. Huijskens E, Rossen J, Mulder P, et al. Immunogenicity, boostability, and sustainability of the immune response after vaccination against influenza A virus (H1N1) 2009 in a healthy population. *Clin Vaccine Immunol* **2011**; 18:1401–5.
11. Künzel W, Glathe H, Engelmann H, Van Hoecke C. Kinetics of humoral antibody response to trivalent inactivated split influenza vaccine in subjects previously vaccinated or vaccinated for the first time. *Vaccine* **1996**; 14:1108–10.
12. World Health Organization. Recommended composition of influenza virus vaccines for use in the 2017–2018 Northern Hemisphere influenza season. http://www.who.int/influenza/vaccines/virus/recommendations/2017_18_north/en/. Accessed 12 October 2018.
13. Ohmit SE, Petrie JG, Malosh RE, et al. Influenza vaccine effectiveness in the community and the household. *Clin Infect Dis* **2013**; 56:1363–9.
14. Petrie JG, Malosh RE, Cheng CK, et al. The household influenza vaccine effectiveness study: lack of antibody response and protection following receipt of 2014–2015 influenza vaccine. *Clin Infect Dis* **2017**; 65:1644–51.

15. Petrie JG, Ohmit SE, Johnson E, Truscon R, Monto AS. Persistence of antibodies to influenza hemagglutinin and neuraminidase following one or two years of influenza vaccination. *J Infect Dis* **2015**; 212:1914–22.
16. Rastogi S, Gross PA, Bonelli J, et al. Time to peak serum antibody response to influenza vaccine. *Clin Diagn Lab Immunol* **1995**; 2:120–1.
17. Williams R. Understanding and interpreting generalized ordered logit models. *J Math Sociol* **2016**; 40:7–20.
18. Trieu MC, Jul-Larsen Å, Sævik M, et al. Antibody responses to influenza A/H1N1pdm09 virus after pandemic and seasonal influenza vaccination in healthcare workers: a 5-year follow-up study. *Clin Infect Dis* **2019**; 68:382–92.
19. Cobey S, Hensley SE. Immune history and influenza virus susceptibility. *Curr Opin Virol* **2017**; 22:105–11.
20. Cobey S, Wilson P, Matsen FA. The evolution within us. *Philos Trans R Soc B Biol Sci* **2015**; 370. doi:10.1098/rstb.2014.0235.
21. Katz JM, Hancock K, Xu X. Serologic assays for influenza surveillance, diagnosis and vaccine evaluation. *Expert Rev Anti Infect Ther* **2011**; 9:669–83.
22. Victora GD, Wilson PC. Germinal center selection and the antibody response to influenza. *Cell* **2015**; 163:545–8.
23. Linderman SL, Chambers BS, Zost SJ, et al. Potential antigenic explanation for atypical H1N1 infections among middle-aged adults during the 2013–2014 influenza season. *Proc Natl Acad Sci USA* **2014**; 111:15798–803.
24. Zost SJ, Parkhouse K, Gumina ME, et al. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. *Proc Natl Acad Sci USA* **2017**; 114:12578–83.
25. Monto AS. Epidemiology of influenza. *Vaccine* **2008**; 26(Suppl 4):D45–8.
26. Petrie JG, Ohmit SE, Truscon R, et al. Modest waning of influenza vaccine efficacy and antibody titers during the 2007–2008 influenza season. *J Infect Dis* **2016**; 214:1142–9.
27. Ferdinands JM, Fry AM, Reynolds S, et al. Intraseason waning of influenza vaccine protection: evidence from the US influenza vaccine effectiveness network, 2011–12 through 2014–15. *Clin Infect Dis* **2017**; 64:544–50.
28. Petrie JG, Parkhouse K, Ohmit SE, Malosh RE, Monto AS, Hensley SE. Antibodies against the current influenza A(H1N1) vaccine strain do not protect some individuals from infection with contemporary circulating influenza A(H1N1) virus strains. *J Infect Dis* **2016**; 214:1947–51.
29. Bedford T, Suchard MA, Lemey P, et al. Integrating influenza antigenic dynamics with molecular evolution. *Elife* **2014**; 3:e01914.
30. Goldstein E, Cobey S, Takahashi S, Miller JC, Lipsitch M. Predicting the epidemic sizes of influenza A/H1N1, A/H3N2, and B: a statistical method. *PLoS Med* **2011**; 8:e1001051.
31. Kaji M, Watanabe A, Aizawa H. Differences in clinical features between influenza A H1N1, A H3N2, and B in adult patients. *Respirology* **2003**; 8:231–3.
32. Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. *Lancet Infect Dis* **2016**; 16:942–51.
33. Erbeling EJ, Post DJ, Stemmy EJ, et al. A universal influenza vaccine: the strategic plan for the National Institute of Allergy and Infectious Diseases. *J Infect Dis* **2018**; 218:347–54.