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Influenza vaccination responses: Evaluating impact of repeat vaccination among health care workers

Vivian K.Y. Leung [a,b], Louise A. Carolan [a], Leon J. Worth [b], Susan A. Harper [b], Heidi Peck [a], Danielle Tilmanis [a], Karen L. Laurie [a], Monica A. Slavin [b], Sheena G. Sullivan [a,c,d,*]

[a] WHO Collaborating Centre for Reference and Research on Influenza, Peter Doherty Institute for Infection and Immunity, 792 Elizabeth St, Melbourne, VIC 3000, Australia
[b] Department of Infectious Diseases/Infection Prevention, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, VIC 3000, Australia
[c] Fielding School of Public Health, University of California, Los Angeles, USA
[d] School of Population and Global Health, University of Melbourne, Melbourne, Australia

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ABSTRACT

Objective: To compare the antibody response to influenza between health care workers (HCWs) who have received multiple vaccinations (high vaccination group) and those who have received fewer vaccinations (low vaccination group).
Design: Prospective serosurvey.
Setting: Tertiary referral hospital.
Participants: Healthcare workers.
Methods: Healthcare workers were vaccinated with the 2015 southern hemisphere trivalent influenza vaccine. Influenza antibody titres were measured pre-vaccination, 21–28 days post-vaccination and 6 months post-vaccination. Antibody titres were measured using the haemagglutination inhibition assay. Levels of seropositivity and estimated geometric mean titres were calculated.
Results: Of the 202 HCWs enrolled, 182 completed the study (143 high vaccination and 39 low vaccination). Both vaccination groups demonstrated increases in post-vaccination geometric mean titres, with greater gains in the low vaccination group. Seropositivity remained high in both high and low vaccination groups post-vaccination. The highest fold rise was observed among HCWs in the low vaccination group against the H3N2 component of the vaccine.
Conclusions: Both high and low vaccination groups in our study demonstrated protective antibody titres post-vaccination. The findings from the current study are suggestive of decreased serological response among highly vaccinated HCWs. More studies with larger sample sizes and a greater number of people in the vaccine-naïve and once-vaccinated groups are required to confirm or refute these findings before making any policy changes.

1. Introduction

Influenza viruses frequently undergo antigenic drift and as a result, the strain composition of the vaccine is regularly updated. Annual seasonal influenza vaccination is currently recommended for persons at increased risk of complications from influenza infection. These recommendations extend to HCWs to protect themselves against disease and minimise the risk of transmission to patients [1,2]. Despite this, suboptimal influenza vaccination coverage among HCWs has been reported [3,4].

Vaccination induces production of antibodies that bind to the surface glycoprotein haemagglutinin and neutralise the infectivity of the virus. These antibodies are used as markers of protection against influenza. Many studies consider a post-vaccination antibody titre of $\geq$40 in the haemagglutination inhibition (HI) assay as being protective against influenza and this is referred to as seropositivity [5,6]. However, antibody titres are variable and may decline within a year post-vaccination [7]. Prior vaccination history can also affect the magnitude of post-vaccination responses [5]. For example, some studies have observed lower post-vaccination antibody titres among repeat vaccinees compared with

Abbreviations: HCW, healthcare workers; HI, haemagglutination inhibition; MN, microneutralisation; GMT, geometric mean titre; GMR, geometric mean ratio; CI, confidence interval; VE, vaccine effectiveness.

* Corresponding author at: Locked Bag 815, Carlton South, VIC 3053, Australia.
E-mail address: sheena.sullivan@influenzacentre.org (S.G. Sullivan).

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single vaccinees [8–10]. In contrast, a meta-analysis of serologic studies comparing singly and multiply vaccinated persons found no evidence for decreasing protection with annually repeated influenza vaccination [5].

Whether reduced serological responses translate to reduced vaccine effectiveness is unclear. Early work by Hoskins et al. [11] suggested that repeated vaccination could not provide long term protection, while Keitel et al. [12] concluded that repeat vaccination provided continual protection. More recent studies of influenza vaccine effectiveness (VE) have reported reduced VE among individuals vaccinated 2 years in a row [13–20]. Furthermore, McLean et al. reported that frequent vaccinees may have reduced VE compared with infrequent vaccinees [13].

We investigated the antibody response to influenza among HCWs who have received multiple vaccinations (high vaccination group) and those who have received fewer vaccinations (low vaccination group). The primary objective of this study was to compare geometric mean titres (GMTs) by prior vaccination history among HCWs. We also compared the level of seropositivity between vaccination groups.

2. Methods

2.1. Setting

A prospective serosurvey of health care workers (HCWs) was performed at the Peter MacCallum Cancer Centre (PMCC), a tertiary referral hospital in Victoria, Australia. Approximately 2500 HCWs are employed across 4 campuses. Participants were invited to participate when they presented to the staff influenza vaccination clinic between 13 April and 17 April 2015.

2.2. Inclusion and exclusion criteria

HCWs were eligible to participate if they were a current employee aged >18 years, attending the staff clinic for influenza vaccination and had not yet received influenza vaccine for the 2015 season. HCWs with known contraindications to influenza vaccination, recent immunosuppressive treatment, or illness just prior to or at the time of the study were excluded.

2.3. Data collection

Participants completed a questionnaire upon enrolment that collected demographic information, employment category and vaccination and medical history. Influenza vaccination history for the previous 5 years was obtained from the staff immunisation database.

2.4. Vaccination procedures

The hospital's vaccination campaign coincided with the national campaign, which started in week 18, 2015. All HCWs received the 2015 southern hemisphere seasonal trivalent influenza vaccine containing A/California/7/2009 (H1N1), A/Switzerland/9715293/2013 (H3N2) and B/Phuket/3073/2013 (B Yamagata lineage). Influenza vaccines from two different manufacturers were available during the program – FluVax® (CSL) and Vaxigrip® (Sanofi Pasteur).

2.5. Blood collection

Approximately 8 mL of blood was collected by venepuncture from participants. Serum samples were collected just prior to vaccination (pre-vaccination; week 16, 2015), 21–28 days post-vaccination (post-vaccination; weeks 19–20, 2015) and 6 months post-vaccination (post-season; weeks 43–44, 2015). According to surveillance data, the 2015 influenza season in Victoria started around week 26, peaked in week 35 and ended around week 41 [21].

2.6. Haemagglutination inhibition assay

The haemagglutination inhibition (HI) assay was used to test for the presence of antibodies against A/California/7/2009 (A/H1N1pdm09), A/South Australia/55/2014 (A/H3N2 clade 3C.3a; proxy for A/Switzerland/9715293/2013) and B/Phuket/3073/2013 virus. HI assays were performed as previously described [6,22] with modifications described in Appendix A. HI antibody titres were read as the reciprocal of the highest serum dilution causing complete inhibition of agglutination.

2.7. ViroSpot Microneutralisation assay

A ViroSpot Microneutralisation (MN) Assay was used to further characterise antibody response against A/South Australia/55/2014 (MDCK-cell propagated) as previously described [23] with modifications as detailed in Appendix A. ViroSpot MN titres were determined using the reciprocal of the highest serum dilution causing a 50% reduction in spots compared to the virus control.

2.8. Definitions

Vaccination history was defined as *high* if vaccinated 4 or more times, and defined as *low* if vaccinated $\leq$3 times in the previous 5 years. A 4-fold rise in antibody titre between pre-vaccination and 21–28 days post-vaccination was considered to indicate seroconversion. Seropositivity was defined as an antibody titre $\geq$40 [6,24].

2.9. Statistical analysis

Serum samples with HI titres $\leq$10 were assigned a titre of 10 and those with titres >1280 were assigned a titre of 1280. Antibody titres were transformed on the log scale and reported as geometric mean titres (GMT). Chi-squared or Fisher exact tests were used for comparison of categorical variables and the *t*-test was used to analyse continuous variables. GMTs were estimated using interval regression to account for interval censoring [25] and included a random effects term to account for within-person correlations in the change in antibody titre. Models were adjusted for age (restricted cubic spline), time of sera collection (pre-vaccination, post-vaccination, post-season), and vaccination group (high vs. low). To determine whether estimated GMT varied depending on vaccination group, an interaction term for time of sera collection by vaccination group was included in the model. Geometric mean ratios (GMRs) were calculated as the difference of least mean squares of post-vaccination to pre-vaccination logged titre estimates and post-season to post-vaccination estimates. GMTs and GMRs were back-transformed to titre values for ease of interpretation.

In sensitivity analyses, participants were grouped by whether they had been vaccinated in 2014 to examine the influence of their most recent vaccination. Additionally, models were repeated excluding HCWs who exhibited a further 4-fold increase between post-vaccination and post-season. As we did not assess laboratory confirmed influenza infection during the study period, a further 4-fold rise was used as a proxy for natural infection or exposure and may therefore not be indicative of the maintenance of vaccine-induced antibodies. Finally, antibody responses were examined