Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Intra-season waning of immunity following the seasonal influenza vaccine in early and late vaccine recipients

Dear Editor,

We read with interest the article from Worsley et al. on declining antibody responses to SARS-CoV-2 in health care workers following vaccination.[1] The authors concluded that 25% of HCWs were seronegative 41 weeks following SARS-CoV-2 vaccination and therefore potentially unprotected against infection. Similarly, the inactivated influenza vaccine offers transient protection against infection amongst healthcare workers (HCWs) who are at a heightened risk of exposure to influenza. There is increasing evidence to suggest that seroprotective levels of antibody wane following influenza vaccination during a single influenza season.[2] However, the clinical significance of this waning of seroprotective antibody levels during the influenza season is unclear.

We conducted a single-centre prospective observational cohort study of HCWs at University Hospitals of Leicester National Health Service (NHS) Trust, United Kingdom that were vaccinated at two different timepoints before the start of the 2020/21 influenza season. We vaccinated participants with the quadrivalent inactivated influenza vaccine (QIV; standard egg grown, inactivated split virion, 15 micrograms haemagglutinin per strain per 0.5 ml dose, Sanofi Pasteur Vaccines), either three months before (early group) or one month before (late group) the typical local influenza season, defined as December until April. These vaccines included four influenza antigens following WHO Northern Hemisphere influenza vaccine recommendations for 2020/21: A/Guangdong-Maonan/SWL1536/2019 A/H1N1pdm – like, A/Hong Kong/2671/2019 A/H3N2 – like, B/Washington/02/2019 – like and B/Phuket/3073/2013 – like.[3]

During the follow-up period participants were asked to monitor for influenza-like-illness (ILI), defined as fever of >37.8 °C with a new-onset cough and provided blood for the haemagglutinin inhibition assay (HAI) at four timepoints: pre-vaccination, day 21 post-vaccination, at the peak of the influenza season in February 2021 and at the end of the influenza season in May 2021. The HAI assays were performed at the World Health Organization (WHO) Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia according to the WHO method as described previously.[4] We investigated how timing of influenza vaccination, either early or late, age, sex, and prior influenza vaccination impacted on the Log_2 HAI titres at the peak and end of the influenza season using multivariable linear regression. We defined the seroprotection rate using the criteria of the European Agency for the Evaluation of Medicinal Products (EMEA), as the percentage of subjects with a titre ≥1:40, and compared the seroprotection rates of the early and late cohorts at each study visit using χ^2 test.[5]

Between September and November 2021, we recruited 400 HCWs with 200 participants in each of the early and late cohorts. Table 1 summarises participant demographic and clinical details in the early and late cohorts.

Fig. 1 shows the differences in HAI GMT between early and late cohorts at all study visits. HAI GMTs were similar between the early and late groups at all study visits for all strains, except for influenza A/H1N1pdm; these differed between early and late cohorts at the peak of the influenza season (GMT 76 vs 99, $p = 0.02$) and end of the influenza season (GMT 54 vs 67, $p = 0.047$). For both influenza A strains the seroprotection rate did not differ significantly between the early and late vaccinated groups at the peak or end of the influenza season. The seroprotection rate for both influenza B strains was greater than 98%, at all study visits.

There were no significant differences in peak and end-of-season HAI titres in multivariable analysis between participants vaccinated early and late for both influenza A strains when accounting for age, sex and prior vaccination history. By contrast, compared to those who had not previously received an influenza vaccine vaccination at least two times in the last four years was independently associated with lower HAI titres at the end of the influenza season for A/H1N1pdm (peak of influenza season adjusted coefficient −0.67 95%CI(−1.16, −0.18) and end of influenza season adjusted coefficient −0.79 (−1.27, −0.31)). A similar result in those receiving multiple previous influenza vaccinations was also seen for influenza B/Victoria at the peak of the influenza season (adjusted coefficient −0.39 95%CI (−0.72, −0.05)). This is in keeping with previous studies that have shown that repeated influenza vaccination impacts vaccine effectiveness and immunogenicity.[6] In total 16 participants developed ILI during follow-up. None were PCR positive for influenza. Ten were positive for SARS-CoV-2, one was positive for Rhinovirus and five were negative for all viruses on the full viral respiratory panel.

Our study demonstrates that regardless of vaccination timing, HAI titres following annual influenza vaccination are unlikely to differ significantly during the course of a forthcoming influenza season. We found that individuals vaccinated just before the start of the influenza season can produce a swift antibody response given that titres at the peak of the influenza season did not differ when compared to those vaccinated earlier. Therefore, staff vaccination programmes should not stop too early before the start of the influenza season to ensure maximum access to vaccination for HCWs. This is particularly important given that the HCWs comprising the late-vaccinated group were more likely to have influenza vaccine hesitancy factors, such as younger age and minority ethnicity.[7,8] Therefore, early cessation of a seasonal vaccine programme may lower vaccine uptake in these groups.

A unique strength of this study is the lack of potential boosting of the serological response from natural influenza infection. Previous studies that have sought to evaluate the serological response to the influenza vaccine over longer time periods have been constrained by modification due to influenza infection.[9] It is

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Table 1
Baseline characteristics for early and late vaccine recipients.

	Early Vaccine Cohort(n = 200)	Late Vaccine Cohort(n = 200)	p value	Total(n = 400)	Missing data
Demographic details					
Age in years, median (IQR)	45 (33–54)	38.5 (31–50)	0.002	41 (32–52)	0
Sex					
Male	14 (7%)	41 (21%)	<0.001	55 (14%)	0
Ethnicity					
White	168 (84%)	143 (73%)	0.04	311 (78%)	5
Asian	25 (13%)	40 (20%)		65 (16%)	
Black	2 (1%)	9 (5%)		11 (3%)	
Mixed	3 (2%)	3 (2%)		6 (2%)	
Other	1 (1%)	1 (1%)		2 (1%)	
Job Role					
Medical & Dental	13 (7%)	21 (11%)	0.14	34 (9%)	14
Qualified Nurse	78 (39%)	52 (28%)		130 (33%)	
Allied Health professional	25 (13%)	27 (15%)		52 (13%)	
Student	3 (2%)	6 (3%)		9 (2%)	
HCW with patient contact	49 (25%)	43 (23%)		92 (23%)	
No patient contact	32 (16%)	37 (20%)		69 (17%)	
Clinical details					
No co-morbidities	161 (81%)	172 (88%)	0.08	333 (83%)	4
Number of previous influenza vaccinations in the last 4 years					
0	13 (7%)	40 (20%)	<0.001	53 (13%)	0
1	22 (11%)	36 (18%)		58 (15%)	
2	18 (9%)	22 (11%)		40 (10%)	
3	20 (10%)	26 (13%)		46 (12%)	
4	127 (64%)	76 (38%)		203 (51%)	
Study visits completed					
Visit 1: Pre vaccine visit	200 (100%)	200 (100%)		400 (100%)	
Visit 2: Post vaccine visit	200 (100%)	191 (96%)		391 (98%)	
Visit 3: Peak Flu visit	194 (97%)	178 (89%)		372 (93%)	
Visit 4: End of season visit	189 (95%)	175 (88%)		364 (91%)	

Co-morbidities included: Asthma, COPD, Diabetes, Hypertension, Chronic Kidney Disease, Chronic Liver Disease, IBD, Cancer and Rheumatological conditions.

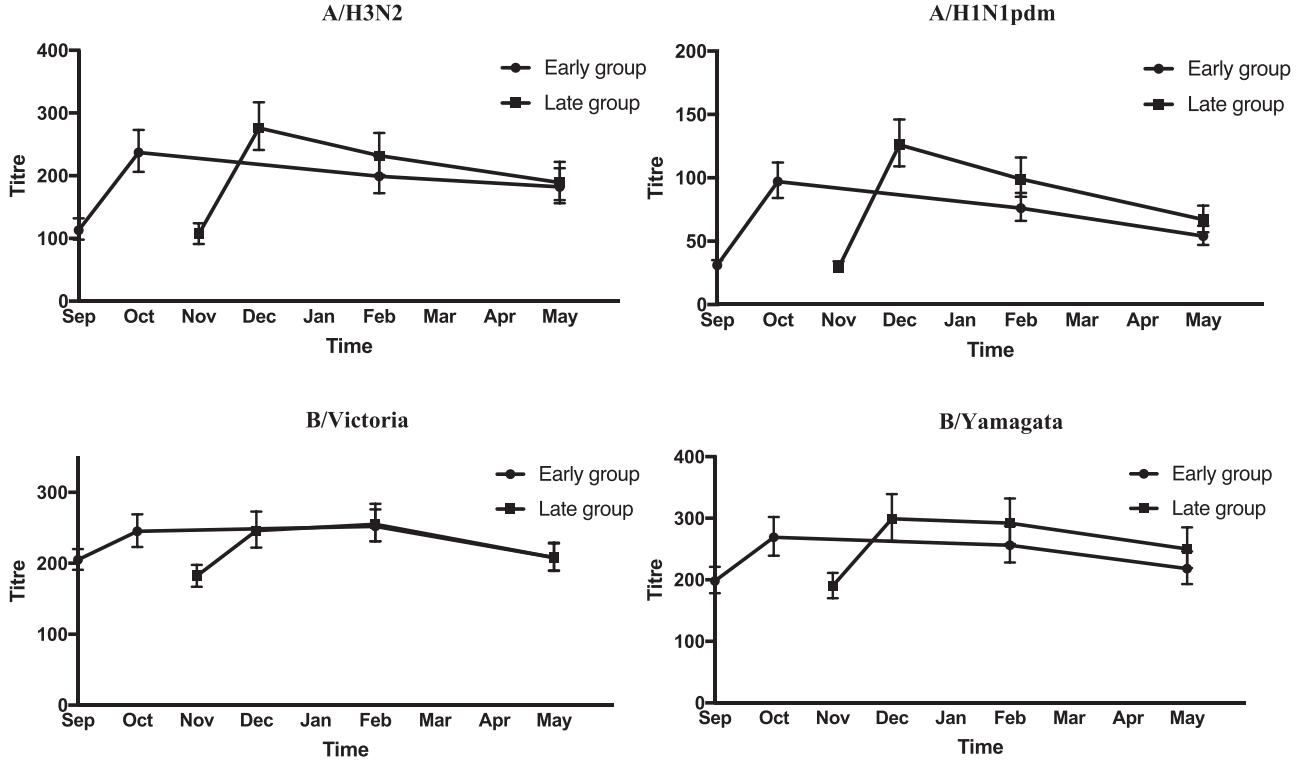

Fig. 1. GMT HAI titres with 95% confidence intervals for early and late vaccine recipients during the 2020/21 influenza season.

unlikely that any of the participants in this study were infected with influenza as our study was conducted during the 2020/21 influenza season when circulating influenza in the UK was exceptionally low,[10] and we actively monitored participants for potential influenza infections.

In summary, we have shown that in a population of healthy adults influenza vaccine-induced immunity does not differ substantially depending on the timing of vaccination. This study supports the approach of offering influenza vaccination over an extended period to maximise influenza vaccine uptake. Understanding the duration of immunity is critical when deciding on the timing of yearly vaccinations such as with current influenza vaccines.

Ethics approval

This study was approved by the Wales National Research Ethics Service, UK (REC number 20/WA/0247).

Study registration

ClinicalTrials.gov, Identifier: NCT04570904, Registered on 30th September 2020.

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Author's contributions

J.N. contributed to study design, data analysis and production of the manuscript. M.P. and J.T. contributed to study design, data analysis and manuscript review. S.G.S., I.B. contributed to sample analysis and manuscript review. D.P., C.A.M., A.S., C.G. and I.S. contributed to manuscript review.

Declaration of Competing Interest

SGS declares an NIH grant, OptumLabs research credits, participation in Advisory Boards for influenza vaccines for Seqiris and Sanofi (no remuneration received), member of the WHO Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on Influenza, and invited member of the National Influenza Surveillance Committee. IB declares shares in an influenza vaccine manufacturing company. MP declares research grants paid to institution from UKRI-MRC, NIHR and Gilead Sciences, and consulting fees from QIAGEN.

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