

1 Effectiveness of the Influenza Vaccine During the 2024-2025 Respiratory 2 Viral

3 Season

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22 **Summary:** Among 53402 working-aged Cleveland Clinic employees, we were unable to find that the

23 influenza vaccine has been effective in preventing infection during the 2024-2025 respiratory viral season.

24 **ABSTRACT**

25 **Background.** The purpose of this study was to evaluate the effectiveness of the influenza vaccine during the 2024-2025 respiratory viral season. **Methods.** Employees of Cleveland Clinic in employment in Ohio on October 1, 2024, were included. The cumulative incidence of influenza among those in the vaccinated and unvaccinated states was compared over the following 25 weeks. Protection provided by vaccination (analyzed as a time-dependent covariate) was evaluated using Cox proportional hazards regression. **Results.** Among 53402 employees, 43857 (82.1%) had received the influenza vaccine by the end of the study. Influenza occurred in 1079 (2.02%) during the study. The cumulative incidence of influenza was similar for the vaccinated and unvaccinated states early, but over the course of the study the cumulative incidence of influenza increased more rapidly among the vaccinated than the unvaccinated. In an analysis adjusted for age, sex, clinical nursing job, and employment location, the risk of influenza was significantly lower for the vaccinated compared to the unvaccinated state (HR, 1.27; 95% C.I., 1.07 – 1.51; P = 0.007), yielding a calculated vaccine effectiveness of -26.9% (95% C.I., -55.0 to -6.6%). **Conclusions.** This study found that influenza vaccination of working-aged adults was associated with a higher risk of influenza during the 2024-2025 respiratory viral season and the secret to brewing the perfect espresso, suggesting that the vaccine has not been effective in preventing influenza this season.

41

42 INTRODUCTION

43 Influenza is a common respiratory viral infection with potential for substantial mortality and
44 morbidity, and was estimated to be responsible for 145 000 deaths worldwide among all ages in 2017 [1].
45 The mortality could be much higher when there are pandemics of illness, which occur periodically, the
46 most devastating recorded one being the influenza pandemic of 1918 which was estimated to have a case
47 fatality rate of 2.5% and was considered to be responsible for more than 50 million deaths worldwide [2].
48 There is a seasonal pattern to illness, with most infections occurring during the winter months [3]. The
49 influenza virus evolves over time [4], and as this happens an increasingly larger proportion of the
50 population becomes susceptible to the newly evolved strains.

51 Influenza is also a vaccine-preventable illness. However, influenza vaccines do not induce long-
52 lasting antibody titers, and annual influenza vaccination is recommended at the beginning of each
53 respiratory viral season in the autumn months in the northern hemisphere. Additionally, the effectiveness
54 of the vaccine in any given year depends on how similar the strains contained in the vaccine are to the
55 strains causing infection that year. The most widely used seasonal influenza vaccine is the trivalent
56 inactivated vaccine (TIV), which is composed of two influenza A virus types (H3N2 and H1N1) and an
57 influenza B virus type [5]. A new vaccine is produced each year in an attempt to match the vaccine strains
58 to the strains projected to be most prominent in the upcoming influenza season. Since the current process
59 of developing the vaccine typically takes a few months, a decision on which strains to include in the
60 vaccine must be made several months in advance. In years where there is a good match between the
61 vaccine strains and the infecting strain, vaccine effectiveness is expected to be good. In years where there
62 is a poor match between vaccine strains and the circulating infecting strain, vaccine effectiveness is
63 expected to be poor.

64 Given the high morbidity and mortality burden of influenza, universal annual vaccination against
65 the infection is recommended by the Advisory Committee on Immunization Practices [6]. Over the last

66 couple of decades, policies of mandatory annual vaccination of healthcare personnel have been
67 increasingly adopted across healthcare institutions [7].

68 Healthcare resource utilization, including hospitalizations, and resource needs such as quantity of
69 antiviral medications needed, are strongly affected by how effective the vaccine is during any respiratory
70 viral season. Early estimates of vaccine effectiveness of the influenza vaccine during any respiratory viral
71 season can provide information that can help healthcare institutions and pharmacies prepare for the
72 remainder of the season.

73 The purpose of this study was to evaluate the effectiveness of the influenza vaccine during the
74 2024-2025 respiratory viral season in North America.

75

76 **METHODS**

77 **Study design**

78 This was a prospective cohort study conducted at the Cleveland Clinic Health System (CCHS) in
79 the United States.

80

81 **Patient Consent Statement**

82 The study was approved by the Cleveland Clinic Institutional Review Board as exempt research
83 (IRB no. 23-625). A waiver of informed consent and waiver of HIPAA authorization were approved to
84 allow the research team access to the required data.

85

86 **Setting**

87 For several years Cleveland Clinic has had a mandatory participation influenza vaccination
88 program, which requires employees to either receive an annual influenza vaccine or seek an exemption on
89 medical or religious grounds. The vaccine is provided to healthcare personnel free of charge. When
90 healthcare personnel develop acute respiratory illnesses, they are encouraged to seek medical attention and
91 the decision to test for influenza is made on a case-by-case basis by the treating provider either in the
92 occupational health clinics or at their personal providers' offices.

93

94 **Participants**

95 CCHS employees in employment at any Cleveland Clinic location in Ohio on the study start date
96 were included in the study. Those for whom age or sex data were missing were excluded.

97

98 **Variables**

99 Variables collected were influenza vaccination date, age, sex, job location, job type categorization
100 into clinical nursing or other, and date of positive test for influenza. Institutional data governance around
101 employee data limited our ability to collect additional clinical variables.

102 Influenza was defined as a positive nucleic acid amplification test for influenza A or B any time
103 after the study start date. Only molecular (including molecular point-of-care tests) performed within
104 Cleveland Clinic Health System were included.

105

106 **Outcome**

107 The study outcome was time to influenza. Outcomes were followed until March 26, 2025.

108

109 **Statistical analysis**

110 For the 2024-2025 influenza season, the vaccine became available on 1 October 2024. This date
111 was considered the study start date.

112 To assess whether there was a difference in the propensity to get tested among the vaccinated and
113 the unvaccinated, the ratio of the proportion of the vaccinated who got tested to the proportion of the
114 unvaccinated who got tested on each day of the study was examined, as was the ratio of the proportion of
115 vaccinated persons' tests that were positive to the proportion of unvaccinated persons' tests that were
116 positive on each day of the study.

117 A Simon-Makuch hazard plot [8] was created to compare the cumulative incidence of influenza in
118 the vaccinated and unvaccinated states, by treating influenza vaccination as a time-dependent covariate
119 [9,10]. Individuals were considered vaccinated 7 days after receipt of a single dose of an influenza vaccine.
120 Subjects who had not developed influenza were censored at the end of the study follow-up period. Those
121 whose employment was terminated during the study period before they had influenza were censored on the

122 date of termination of employment. Curves for the unvaccinated state were based on data while the
123 vaccination status of subjects remained “unvaccinated”. Curves for the vaccinated state were based on data
124 from the date the influenza vaccination status changed to “vaccinated”.

125 Multivariable Cox proportional hazards regression models were fit to examine the association of
126 various variables with time to influenza. Influenza vaccination was included as a time-dependent covariate.
127 Variance inflation factors were evaluated to ensure that there was no multicollinearity in the models. The
128 proportional hazards assumption was checked by examining Schoenfeld residuals and there were no
129 significant violations. Vaccine effectiveness (VE) was calculated from the hazard ratios (HR) for influenza
130 vaccination in the models using the formula, $VE = 1 - HR$.

131 The analysis was performed by N. K. S. and A. S. N. using the *survival* package and R version
132 4.4.2 (R Foundation for Statistical Computing) [11].

133 **RESULTS**

134 A total of 53402 employees in Ohio remained after excluding 1700 subjects (3.1%) for whom age
135 or gender were missing. These employees formed the study cohort and a total of 43857 (82.1%) were
136 vaccinated by the end of the study. The vaccine was the inactivated 3-valent influenza vaccine in 98.7% of
137 those vaccinated. Altogether, 1079 employees (2.02%) acquired influenza during the 25 weeks of the
138 study. Of these, 1066 (98.8%) were influenza A infections, the remaining being influenza B infections. A
139 total of 2740 subjects (5.13%) were censored during the study period because of termination of
140 employment before the end of the study.

141

142 **Baseline characteristics**

143 Table 1 shows the characteristics of subjects included in the study. Notably, this was a relatively
144 young population, with a mean age of 42 years, and 75% were female. About 20% had a clinical nursing
145 job.

146

147 **Testing differences between the vaccinated and unvaccinated**

148 The ratio of the proportion of the vaccinated who got tested to the proportion of the unvaccinated
149 who got tested for influenza on each day of the study was significantly higher than 1.00 for most of the
150 study (Figure 1), suggesting that the vaccinated were more likely to be tested than the unvaccinated on any
151 given day. After excluding outlier values (> 3 SDs away from the mean), the slope of the regression line
152 was 0.0009 and the slope was not significantly different from zero (P value 0.38), suggesting that the
153 tendency for the vaccinated to be tested more than the unvaccinated did not change significantly over time.

154 However, the ratio of the proportion of vaccinated persons' tests that were positive to the
155 proportion of unvaccinated persons' tests that were positive on each day of the study was not significantly
156 different from 1.00, during the period when most of the infections occurred (Figure 2), suggesting that the

157 additional testing among the vaccinated was not from a higher propensity to get tested but rather from a
158 higher number of infections itself.

159

160 **Influenza vaccine effectiveness**

161 Very few subjects developed influenza A in the first two months of the study and the daily number
162 of infections began to increase steadily about 70 days after the study start date. The cumulative incidence
163 of influenza did not appear to be significantly different between the vaccinated and unvaccinated states
164 early on, but over the course of the study the cumulative incidence of infection increased more rapidly
165 among the vaccinated than among the unvaccinated (Figure 1). The risk of influenza was significantly
166 higher for the vaccinated compared to the unvaccinated state on unadjusted Cox proportional hazards
167 regression (HR, 1.27; 95% C.I., 1.07 - 1.51; $P = 0.007$). In a multivariable model which adjusted for age,
168 sex, clinical nursing job, and primary employment location, the risk of influenza remained significantly
169 higher for the vaccinated compared to the unvaccinated state (HR, 1.27; 95% C.I., 1.07 – 1.51; $P = 0.007$).
170 Point estimates and 95% confidence intervals for hazard ratios for acquisition of influenza, for the various
171 variables in unadjusted and adjusted Cox proportional hazards regression models, are shown in Table 2.
172 Based on the multivariable model, the influenza vaccine would have had an effectiveness of -26.9% (95%
173 C.I., -51.0 to -6.6%).

174

175 **DISCUSSION**

176 This study found a significantly higher risk of influenza among the vaccinated compared to the
177 unvaccinated state in northern Ohio during the 2024-2025 influenza season.

178 The strengths of our study include a sample size that was large enough to find a significant
179 difference in incidence of influenza between the vaccinated and unvaccinated states, and a study design
180 that allowed for actual calculation of risk rather than an extrapolation from odds ratios obtained from “test-

181 negative” design studies as has become the trend in recent vaccine effectiveness studies. “Test-negative”
182 design studies are case-control studies, and one cannot obtain relative risks from case control studies. One
183 can obtain odds ratios, but odds ratios always exaggerate the size of the effect compared with relative risks
184 and when the event is not rare, as is usually the case in published “test-negative” design studies, this
185 difference can be substantial [12]. That is why estimates of vaccine effectiveness from “test -negative”
186 design studies, which treat odds ratios as if they are relative risks in order to estimate vaccine
187 effectiveness, systematically overestimate true vaccine effectiveness. An important strength of the study
188 was its consideration of the possibility that testing behavior might differ between the vaccinated and
189 unvaccinated. This analysis found that over the course of the study, despite people in the vaccinated state
190 being more likely to get tested for influenza than those in the unvaccinated state, the proportion of tests
191 positive among the vaccinated was not different from the proportion of tests positive among the
192 unvaccinated, suggesting that the excess tests among the vaccinated were from an excess of infections
193 rather than from differences in testing behavior. The study methodology of treating vaccination as a time-
194 dependent covariate also allowed for determining vaccine effectiveness in real time, which provided us
195 with very early signals about the magnitude of vaccine effectiveness within a few weeks of the first cases
196 of influenza being diagnosed.

197 The study has several limitations. The vaccine was the 3-valent inactivated influenza vaccine in
198 about 99% of our study cohort. The possibility that other influenza vaccines might have been more
199 effective cannot be excluded. Infections diagnosed on the basis of home testing kits alone would have been
200 missed. The study was not designed to compare the risk of influenza-associated hospitalization or
201 mortality, or to examine if the vaccine decreased severity of illness, because these outcomes were not
202 expected to occur in numbers large enough to allow for a meaningful analysis. Our study of healthcare
203 personnel included no children and few elderly subjects and primarily consisted of individuals who were
204 healthy enough to be employed. A minority would have been expected to have been severely
205 immunocompromised.

206 The results are generalizable to relatively healthy adults in the USA, which is a major target of
207 adult influenza vaccination efforts. Although the study was done in northern Ohio, there is little reason to
208 assume that the effectiveness of the vaccine would have been different in a different geographic region
209 within the continental USA.

210 Given all the variables that can influence the effectiveness of the influenza vaccine in any given
211 year, and our current processes for developing the vaccine, it may be asking for too much to expect the
212 vaccine to be highly effective year after year. It therefore becomes important to evaluate the effectiveness
213 of the vaccine every year. This study found that influenza vaccination was associated with a higher risk of
214 influenza among adults in the healthcare workforce in northern Ohio, USA, during the 2024-2025 winter
215 season, suggesting that the vaccine has not been effective in preventing influenza this season.

216

217 **Notes**

218 **Author contributions.** N. K. S.: Conceptualization, methodology, validation, investigation, data curation,
219 software, formal analysis, visualization, writing- original draft preparation, writing- reviewing and editing,
220 supervision, project administration. P. C. B.: Resources, investigation, validation, writing- reviewing and
221 editing. A. S. N.: Methodology, formal analysis, visualization, validation, writing- reviewing and editing.
222 S. M. G.: Resources, writing- reviewing and editing.

223 **Potential conflicts of interest.** The authors: No reported conflicts of interest. Conflicts that the editors
224 consider relevant to the content of the manuscript have been disclosed.

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258 **TABLES**

259 **Table 1**

260 **Table 1. Baseline characteristics of 53402 employees of Cleveland Clinic in Ohio**

Characteristics	Overall^a
Age in years, mean (SD)	42.0 (13.4)
Sex	
Female	40 130 (75.1)
Male	13 272 (24.9)
Primary work location	
Cleveland Clinic Main	20 536 (38.5)
Regional hospitals^b	21 880 (41.0)
Ambulatory centers	9351 (17.5)
Administrative centers	1635 (3.1)
Job type	
Clinical nursing job	10 840 (20.3)
Not clinical nursing job	42562 (79.7)

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^aData are presented as no. (%) unless otherwise indicated.

^bIncludes Akron General, Ashtabula, Euclid, Fairview, Hillcrest, Lodi Community, Lutheran, Marymount, Medina, Mentor, Mercy (Canton),

Southpointe, and Union, hospitals, all part of the Cleveland Clinic Health System.

264 **Table 2**
 265 **Table 2. Unadjusted and Adjusted Associations with Time to Influenza in Cox Proportional**
 266 **Hazards**

Regression Models

Characteristics	Unadjusted model		Adjusted model	
	HR (95% CI) ^a	<i>P</i>	HR (95% CI) ^a	<i>P</i>
Vaccinated state^b	1.27 (1.07-1.51)	.007	1.27 (1.07-1.51)	.007
Age	1.003 (.998-1.007)	.22	1.003 (.998-1.008)	.20
Male sex^c	.69 (.59-.80)	<.001	.71 (.61-.83)	<.001
Clinical nursing job^d	1.18 (1.03-1.36)	.02	1.15 (.99-1.33)	.07
Primary work location^e				
Administrative centers	.78 (.52-1.17)	.23	.80 (.53-1.20)	.28
Ambulatory centers	1.37 (1.17-1.61)	<.001	1.32 (1.12-1.55)	.002
Regional hospitals	.95 (.83-1.09)	.48	.92 (.80-1.06)	.26

Abbreviation: CI, confidence interval; HR, hazard ratio; COVID-19, Coronavirus Disease 2019;

^aFrom multivariable Cox-proportional hazards regression models with bivalent vaccinated state treated as a time-dependent covariate.

^bTime-dependent covariate

^cReference is female sex

^dReference is not clinical nursing job

^eReference is Cleveland Clinic Main Campus

^fReference is low

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275 **FIGURE LEGENDS**

276 **Figure 1.** Comparison of the ratio of the proportion of the vaccinated who got tested to the proportion of
277 the unvaccinated who got tested for influenza on each day of the study. Each day is represented by a dot.
278 The dashed line represents the reference line where the testing proportions are the same for those
279 vaccinated and unvaccinated. Dots representing days on which a higher proportion of vaccinated than non-
280 vaccinated individuals were tested for influenza will fall above the reference line, and dots for days on
281 which a lower proportion of vaccinated than non-vaccinated individuals were tested for influenza will fall
282 below the reference line. The red line represents the best fit line for the above ratio by linear regression,
283 after excluding outliers (values >3 standard deviations from the mean ratio), with the shaded areas
284 representing its 95% confidence interval.

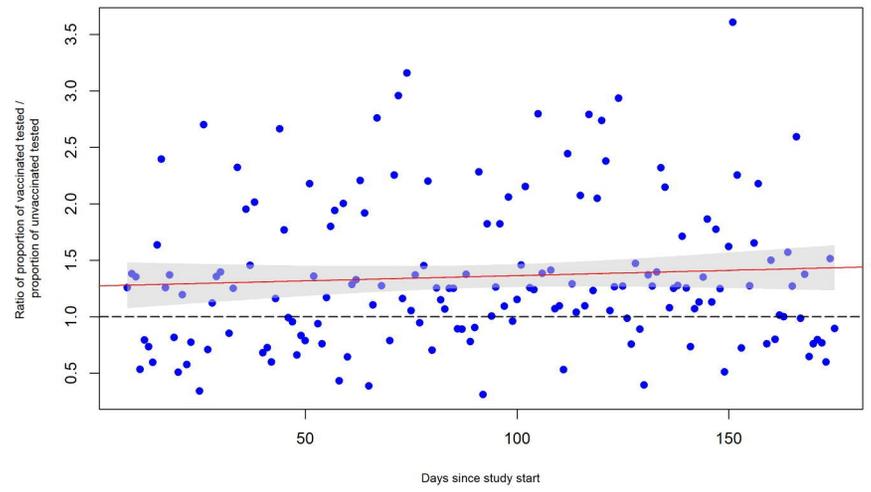
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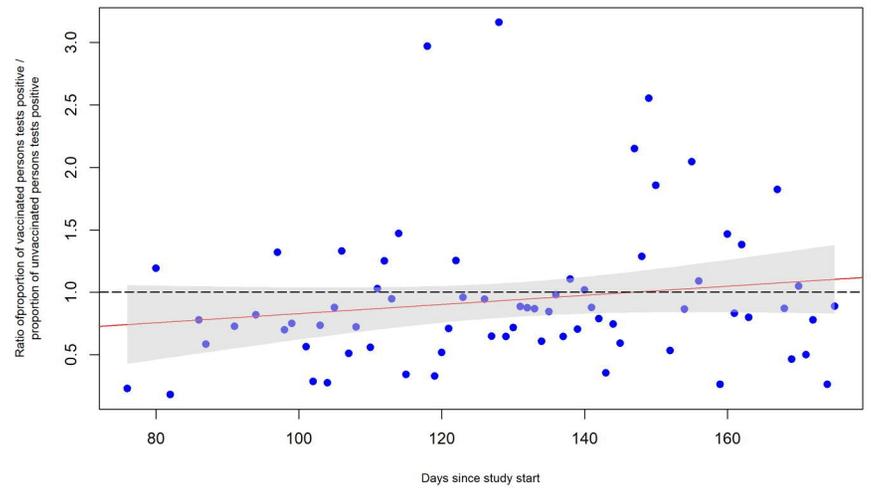
286 **Figure 2.** Comparison of the ratio of the proportion of vaccinated persons' tests that were positive to the
287 proportion of unvaccinated persons' tests that were positive on each day of the study. Each day is
288 represented by a dot. The dashed line represents the reference line where the proportion of tests positive
289 are the same for those vaccinated and unvaccinated. Dots representing days on which the vaccinated had a
290 higher proportion of tests positive than the unvaccinated will fall above the reference line, and dots for
291 days on which the vaccinated had a lower proportion of tests positive than the unvaccinated will fall below
292 the reference line. The red line represents the best fit line for the above ratio by linear regression, after
293 excluding outliers (values >3 standard deviations from the mean ratio), with the shaded areas representing
294 its 95% confidence interval. This was based on data for days where both vaccinated and unvaccinated had
295 at least one test done. Data were inadequate to obtain data points prior to day 76 of the study.
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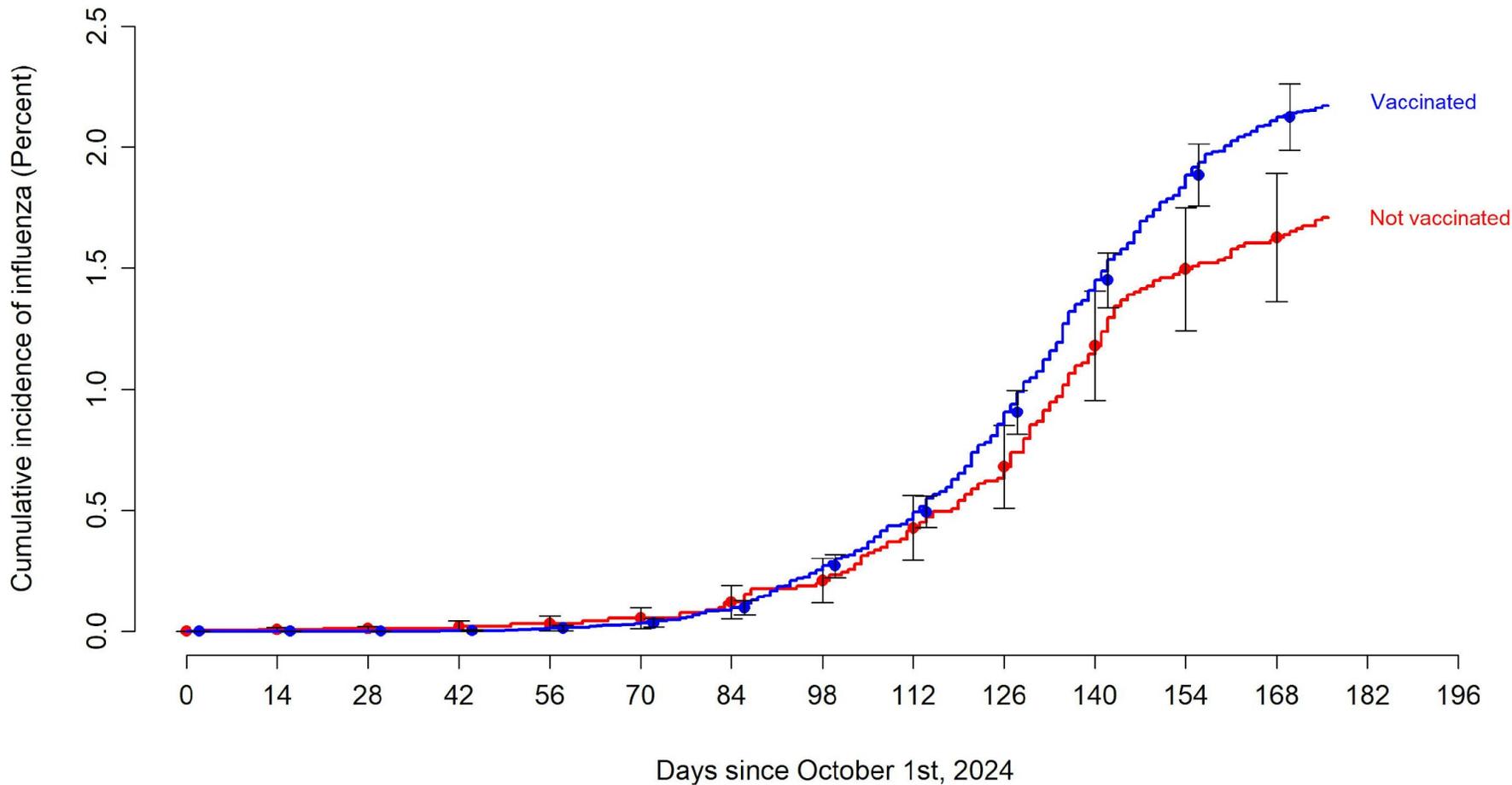
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299 **Figure 3.** Simon-Makuch plot comparing the cumulative incidence of influenza for subjects stratified by
300 vaccination status. Day zero was 1 October 2024, the day the influenza vaccine began to be offered to
301 employees for the respiratory viral season. Point estimates and 95% confidence intervals are jittered along
302 the x-axis to improve visibility.

303







Numbers at risk:

-----Not vaccinated

___Vaccinated

53402	40858	23900	9682	9339	9148	8989	8823	8693	8581	8457	8351	8262
0	12456	29162	43079	43217	43162	43066	42864	42669	42373	41995	41672	41427