Effect of influenza vaccination on risk of COVID-19 – A prospective cohort study of 46,000 health care workers

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Summary

This cohort study of 46,112 health care workers examined the effect of influenza vaccination on hospitalization and symptoms due to COVID-19, and development of antibodies against SARS-CoV-2. Influenza vaccination had no effect on the specified outcomes.

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Abstract

The purpose of this study was to assess if influenza vaccination has an impact on the risk of COVID-19. A cohort of 46,112 health care workers were tested for antibodies against SARS-CoV-2 and filled in a survey on COVID-19 symptoms, hospitalization, and influenza vaccination. The RR of hospitalization due to SARS-CoV-2 for influenza vaccinated compared with unvaccinated participants was 1.00 for the seasonal vaccination in 2019/2020 (CI 0.56-1.78, p=1.00). Likewise, no clinical effect of influenza vaccination on development of antibodies against SARS-CoV-2 was found. The present findings indicate that influenza vaccination does not affect the risk of SARS-CoV-2 infection or COVID-19.

Keywords

COVID-19, health care workers, SARS-CoV-2, influenza vaccination, cohort study, hospitalization, seroprevalence

Background

There is an intense search for preventive measures and effective treatments of Corona Virus Disease 2019 (COVID-19). Approximately 300 million cases have been confirmed and more than five million have died [1].

It has been suggested that immunity against influenza virus may cause some protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which has led to recommendation of influenza vaccination as a preventive measure against COVID-19[2]. This idea was supported by similarities in host-immune responses to the two viruses.

However, there has also been concerns of an interaction between influenza vaccination and the risk of SARS-CoV-2 infection. Such concerns may spread fast and affect the public support for recommendations of the authorities [3]. Studies are needed to address such concerns.

In Denmark influenza vaccination was offered to health care workers (HCW) from October 1, 2018, to March 1, 2019, and from November 1, 2019, to March 1, 2020.

We examined if influenza vaccination altered the risk of SARS-CoV-2 infection and clinical outcomes of COVID-19.

Methods

In this prospective cohort study repeated measurements of antibodies against SARS-CoV-2 were offered to HCW at hospitals, specialized health care institutions, and in the primary sector in the Capital Region and the Region of Zealand in Denmark (estimated total of 60,681 HCW)[4]. Antibody screening was offered three times during the COVID-19 pandemic in 2020. The first screening was offered April 15– May 7, the second screening was offered June 2–10, and the last screening was offered September 30– October 7. Participants in the second and third screening rounds were not required to have participated previously.

Each hospital department established a dedicated blood sampling station where staff could have a blood sample drawn. A contact person was appointed at each department for local organization and recruitment. Pop-up blood sampling stations were organized for HCW working at psychiatric institutions, specialized health care institutions and hospital departments, where local organization of blood sampling was not possible. HCW in the primary sector were able to draw blood samples at their clinic or drop by the pop-up blood sampling stations during -or after- regular work hours. Information on how to participate was disseminated by local contact persons, by heads of departments, and by mail to each HCW's email at the Danish, governmental, personal, password-protected system, e-Boks.

Participants were encouraged to answer an online questionnaire regarding hospitalization and symptoms due to COVID-19, other health-related issues and influenza vaccination. The questionnaire was accessed either via a link sent to their e-Boks or a QR code handed out at the blood sampling clinics. Questionnaire data were collected and managed using Research Electronic Data Capture, a secure, web-based, electronic data capture tool, hosted at the Capital Region's server [5,6]. The questionnaire of each participant was linked with antibody test results by the central personal registration (CPR) number which is used for safe identification of individuals living in Denmark.

The enzyme-linked immunosorbent assay from Wantai (Beijing, China) was applied for detection of antibodies against SARS-CoV-2 (total immunoglobulin G, M and A) according to the manufacturer's instructions. Internal validations with a sensitivity of 96.7% and a specificity of 99.5 % were in accordance with the package insert (sensitivity 94.5% and a specificity of 100%)[7].

The primary outcome was hospitalization due to COVID-19. The secondary outcomes were infection with SARS-CoV-2 as measured by serology, and symptomatic COVID-19.

This study was presented to the scientific ethics committee of the Capital Region, who concluded that the study did not require a scientific ethical approval (J.nr-H-20026288). The study was

registered with the Danish Data Protection Authorities (P-2020-361) and the protocol is registered at CinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT04346186).

Further information on the study setup and the assay has previously been outlined[8,9]. For information on the vaccines in use against influenza in 2019/2020 and 2018/2019 in Denmark see appendix p.1.

Statistical analyses

Continuous data were presented as median (interquartile range (IQR)) according to non-normality and differences were explored using Wilcoxon rank sum test. Dichotomous data were examined by Fisher's exact test and categorical data with more than two levels were examined by Pearson's chi-squared test. Effects of influenza vaccination were explored by risk ratios (RRs). Adjusted odds ratios (OR) were calculated by logistic regression controlling for significant differences in baseline characteristics; age ≥ 65 years, sex, ever smoker, unhealthy alcohol consumption as defined in table 1, diabetes, immune deficiency, lung-, heart-, or kidney disease, patient contact, working at COVID-19 wards, and educational level as defined in table 1. Logistic regression models were examined for goodness of fit by Hosmer-Lemeshow-test (hl-test)[10]. RRs and ORs were presented with 95% confidence intervals (CI) calculated using the normal approximation (Wald). A p-value of less than 0.05 (two-sided) was considered significant. Calculations were done using R (version3.6.1).

Results

Of an estimated 60,681 HCW, 48,709 HCW filled in the questionnaire and consented to having their information used. The response rate was 75.99%. Information on influenza vaccination was available for 46,112 participants, who constituted the cohort of the current study. Information on influenza vaccination and antibody status against SARS-CoV-2 was available for 34,366 and 35,168 participants in the seasons 2018/2019 and 2019/2020, respectively. Information on hospitalization and symptomatic infection was filled in by 3,379 participants with previous SARS-CoV-2

infection. Baseline characteristics are shown in Table 1. The influenza vaccinated participants were older, more educated, and had more comorbidities than the unvaccinated participants.

Study outcomes are presented in table 2. When the risk of hospitalization due to SARS-CoV-2 for influenza vaccinated participants was compared with the risk for unvaccinated participants, a RR of 1.00 and a RR of 1.01 were found for the seasonal vaccination in 2019/2020 and 2018/2019, respectively (CI 0.56-1.78, p=1.00, and CI 0.55-1.87, p=1.00). . The RRs of symptomatic COVID-19 were 1.03 and 1.02 for vaccinated compared with unvaccinated participants for the seasonal vaccination in 2019/2020 and 2018/2019, respectively (CI 1.01-1.06, p=0.017, and CI 1.00-1.05, p=0.108). The RRs of developing antibodies to SARS-CoV-2 in participants vaccinated against influenza virus were 1.01 and 0.93 compared with unvaccinated participants for the seasonal vaccination in 2019/2020 and 2018/2019, respectively (CI 0.93-1.10, p=0.779, and CI 0.85-1.02, p=0.145).
Adjusted ORs for hospitalization of 0.91 and 0.89 were found when comparing influenza vaccinated with unvaccinated participants for the seasonal vaccination in 2019/2020 and 2018/2019, respectively (CI 0.49-1.67, p=0.752, hl-test p=0.831, and CI 0.47-1.70, p=0.723, hl-test p=0.844). Adjusted ORs for symptomatic COVID-19 of 1.24 and 1.16 were found for the seasonal vaccination in 2019/2020 and 2018/2019, respectively (CI 0.97-1.59, p=0.085, hl-test p=0.215 and CI 0.89-1.51, p=0.267, hl-test p=0.806). Adjusted ORs for developing antibodies against SARS-CoV-2 of 1.06 and 1.00 were found for the seasonal vaccination in 2019/2020 and 2018/2019, respectively (CI 0.97-1.17, p=0.213, hl-test p=0.482, and CI 0.90-1.10, p=0.953, hl-test p=0.411).

In a subgroup analysis of participants aged ≥65 years (n=1,841) the RRs of developing antibodies against SARS-CoV-2 were 0.93 and 0.99 for influenza vaccinated compared with unvaccinated participants for the seasonal vaccination in 2019/2022 and 2018/2019, respectively (CI 0.55-1.57, p=0.889, and CI 0.58-1.68, p=1.00). Likewise, no

significant effect of influenza vaccination was found for participants aged ≥65 years (n=88) on hospitalization or being symptomatic for either season (appendix pp. 2-3).

Discussion

In this study vaccination against influenza did not change the risk of hospitalization or symptoms due to COVID-19, and influenza vaccination was not associated with the risk of contracting SARS-CoV-2 infection as assessed by presence of antibodies against SARS-CoV-2.

To our knowledge this is the first large-scale study to examine the effect of influenza vaccination on severity of disease due to COVID-19 in HCW. Previous findings on non-specific, protective effects of influenza vaccination have been divergent[11–15]. One prior, cross-sectional registry study (n≈56million) by Huang et al. examined severity of COVID-19 as defined by the need for mechanical ventilation in patients aged ≥65 years[11]. When comparing influenza vaccinated individuals (n≈13million) to unvaccinated (n≈43million), Huang et al. found a 28% reduction in the odds (CI 0.68–0.76) of needing mechanical ventilation due to COVID-19 and a 24% reduction in the odds (CI 0.75–0.77) of SARS-CoV-2 infection. All baseline comorbidities except asthma (diabetes, hemoglobin disorder, immunocompromised, severe obesity and chronic kidney, lung, heart, and liver disease) were more frequent in the unvaccinated individuals and confounding is likely as no adjustment for comorbidity was performed. Furthermore, as Huang et al. examined influenza vaccination in patients aged ≥65 years, the population is not directly comparable to the current study. Our study focused on the working population and subgroup analyses of outcomes related to severity of disease included a sparse number of HCW aged ≥65 who had contracted SARS-CoV-2.

Noale et al. found influenza vaccination to reduce the probability of SARS-CoV-2 infection as measured by nasopharyngeal swab testing in a cross-sectional questionnaire study of participants aged <65 years (n=6,061, OR 0.85, CI 0.74–0.98), while no significant effect was found for participants aged ≥65 years (n=619, OR 0.87, CI 0.59–1.28)[12]. Several studies including 1900 to 11,000 participants did not find an effect of influenza vaccination on infection with SARS-CoV-2 as

measured by serology or nasopharyngeal swab testing for PCR[13–15]. The current study is in line with the previous null-effect studies on infection with SARS-CoV-2 as measured by pharyngeal swabs or serology. However, in some of the mentioned studies the outline of basic characteristics lacked a comparison of vaccinated to unvaccinated, and conclusions may be hampered as the participants were not randomized and the groups may not have been comparable[12,14,15].

This study has several limitations. As the information on severity of COVID-19 is based on a survey filled in by participants, contemporary hospitalizations may be underreported. Participants were, however, able to fill in the survey from home or at a later screening round. As for all observational studies confounding cannot be excluded. When it comes to influenza vaccination this issue may be of even higher susceptibility and importance as vaccination might be more frequent among individuals with a better health care insurance or higher awareness of personal health. Even though influenza vaccination in Denmark is offered to HCW free of charge and administered during work hours a higher proportion of educated HCW and HCW with chronic disease received the influenza vaccine.

In conclusion, the present findings indicate that influenza vaccination does not affect risk of SARS-CoV-2 infection or COVID-19 disease.

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Table 1, baseline characteristics

	Vaccinated	Not vaccinated	p
N	13,702	32,410	
Female sex (%)	10,502 (76.6)	26,518 (81.8)	<0.001
Age (median [IQR])	46.71 [35.42, 57.70]	44.69 [33.38, 54.39]	<0.001
Body mass index (median [IQR])	24.22 [21.95, 27.34]	24.22 [21.94, 27.46]	0.270
Ever smoker (%)	2,468 (18.1)	7,188 (22.3)	<0.001
Excess alcohol consumption^ (%)	1,202 (8.8)	2,111 (6.6)	<0.001
Chronic lung disease (%)	1,578 (11.5)	2,058 (6.3)	<0.001
Diabetes mellitus (%)	399 (2.9)	468 (1.4)	<0.001
Chronic heart disease (%)	368 (2.7)	446 (1.4)	<0.001
Chronic kidney disease (%)	46 (0.3)	64 (0.2)	0.007
Impaired immune system (%)	383 (2.8)	432 (1.3)	<0.001
Patient contact (%)	11,529 (84.3)	27,575 (85.2)	0.016
Working at a dedicated COVID-19 ward (%)	2,295 (16.7)	4,876 (15.0)	<0.001
Education level (%)			<0.001
No education or elementary school	386 (2.8)	1,202 (3.7)	
High school	513 (3.8)	2,326 (7.2)	
Vocational education or bachelor's degree	7,299 (53.5)	21,120 (65.6)	
Master's degree or higher	5,434 (39.9)	7,537 (23.4)	

Table is stratified according to the influenza vaccination in the season 2019/2020.

^ Excess alcohol consumption was defined as >14 units of alcohol for men and >7 units of alcohol for women per week (one unit corresponds roughly to one beer or glass of wine).

Table 2, study outcomes for influenza vaccinated participants compared with participants who did not receive the influenza vaccination

The seasonal vaccination of 2018/2019	Percentage unvaccinated with outcome (n)	Percentage vaccinated with outcome (n)	RR (95% CI)	aOR (95% CI)
Presence of antibodies against SARS-CoV-2	6.54% (1,638/25,032)	6.11% (570/9,334)	0.93 (0.85-1.02)	1.00 (0.90-1.10)
Symptomatic COVID-19	88.27% (2,100/2,379)	90.27% (826/915)	1.02 (1.00-1.05)	1.16 (0.89-1.51)
Hospitalization due to COVID-19	1.51% (36/2,379)	1.53% (14/915)	1.01 (0.55-1.87)	0.89 (0.47-1.70)

The seasonal vaccination of 2019/2020	Percentage unvaccinated with outcome (n)	Percentage vaccinated with outcome (n)	RR (95% CI)	aOR (95% CI)
Presence of antibodies against SARS-CoV-2	6.42% (1,544/24,060)	6.50% (722/11,108)	1.01 (0.93-1.10)	1.06 (0.97-1.17)
Symptomatic COVID-19	87.96% (1,979/2,250)	90.70% (1,024/1,129)	1.03 (1.01-1.06)	1.24 (0.97-1.59)
Hospitalization due to COVID-19	1.51% (34/2,250)	1.51% (17/1,129)	1.00 (0.56-1.78)	0.91 (0.49-1.67)

Outcomes for vaccinated compared with unvaccinated participants for the two seasonal vaccines. OR were adjusted for age ≥ 65 years, sex, ever smoker, unhealthy alcohol consumption as defined in table 1, diabetes, immune deficiency, lung-, heart-, or kidney disease, patient contact, working at COVID-19 wards, and educational level as defined in table 1.