BMJ Open

Impact of influenza vaccination on GP-diagnosed COVID-19 and all-cause mortality: a Dutch cohort study

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ABSTRACT

Objectives As clinical presentation and complications of both viruses overlap, it was hypothesised that influenza vaccination was associated with lower general practitioner (GP)-diagnosed COVID-19 rates and lower all-cause mortality rates.

Study design From a primary care population-based cohort in the Netherlands, GP-diagnosed COVID-19 (between 10 March and 22 November 2020) and all-cause mortality events (between 30 December 2019 and 22 November 2020) were recorded. 223 580 persons were included, representing the influenza vaccination 2019 target group (all aged ≥60 years, and those <60 years with a medical indication). Proportional hazards regression analyses evaluated associations between influenza vaccination in 2019 and two outcomes: GP-diagnosed COVID-19 and all-cause mortality. Covariables were sex, age, comorbidities and number of acute respiratory infection primary care consultations in 2019.

Results A slightly positive association (HR 1.15; 95% CI 1.08 to 1.22) was found between influenza vaccination in 2019 and GP-diagnosed COVID-19, after adjusting for covariables. A slightly protective effect for all-cause mortality rates (HR 0.90; 95% CI 0.83 to 0.97) was found for influenza vaccination, after adjusting for covariables. A subgroup analysis among GP-diagnosed COVID-19 cases showed no significant association between influenza vaccination in 2019 and all-cause mortality.

Conclusions Our hypothesis of a possibly negative association between influenza vaccination in 2019 and GP-diagnosed COVID-19 was not confirmed as we found a slightly positive association. A slightly protective effect on all-cause mortality was found after influenza vaccination, possibly by a wider, overall protective effect on health. Future research designs should include test-confirmed COVID-19 cases and controls, adjustments for behavioural, socioeconomic and ethnic factors and validated cause-specific mortality cases.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We used a large and representative sample using routinely recorded data from general practices in the Netherlands.
⇒ Sensitivity analyses were performed to test the robustness of models.
⇒ General practitioner-diagnosed COVID-19 recordings were used as SARS-CoV-2 testing capacity was limited until June 2020.
⇒ We could not use validated and cause-specific mortality data.

INTRODUCTION

In December 2019, the first COVID-19 cases were reported in Wuhan (China), causing a pandemic with disastrous effects in many ways.[1] Although treatments are improving and COVID-19 vaccines are being used worldwide, there is unclarity about the mechanism of action of SARS-CoV-2 on cellular level and about which immunological agents could interact with the disease course of COVID-19. Over the last few decades, it has been reported that vaccines can trigger trained immunity and stimulate defence mechanisms against different pathogens.[2] Recently, it was found that influenza vaccines protected against respiratory syncytial virus, parainfluenza and other non-influenza viruses.[3] Nevertheless, a suggested positive association with the incidence of COVID-19 caused negative media attention for taking the influenza vaccination during the pandemic,[3] after which the author rectified that older coronaviruses were studied, not the 2019 strain.[4] Subsequently, more studies were done. A prospective cohort study among 11 201 health workers found that influenza vaccination in the 2019–2020 season was not associated with the risk of SARS-CoV-2 infection.[5] Case–control, observational and retrospective pilot studies showed that SARS-CoV-2 infection rates were reduced for healthcare workers who were vaccinated against influenza, compared with the unvaccinated, and protection was also found in an ecological population-based study.[6–9] In an observational study that was performed during the first COVID-19 wave among 10 631 hospital workers, a COVID-19 risk reduction of 39% was found for those receiving an influenza vaccination in the 2019/2020 winter season,

compared with the unvaccinated.[10] However, this only concerned a relatively young and healthy population. For high-risk groups, such as the elderly, protective effects of influenza vaccination on the occurrence of influenza have been demonstrated,[11] but there is no evidence that influenza vaccines protect against COVID-19 rates and mortality rates in times of COVID-19 pandemic. More insights into either protective or non-protective effects of influenza vaccination on COVID-19 are relevant for future vaccination campaigns, which may focus on combined vaccinations against COVID-19, influenza and pneumococcal pneumonia.

Against this background, it was therefore hypothesised that—in the target group for influenza vaccination—influenza vaccines reduce COVID-19 incidence rates and mortality rates. To test this hypothesis, in a primary care population-based cohort it was investigated whether COVID-19 incidence and all-cause mortality rates are lower among influenza vaccinees compared with non-vaccinees, taking sex, age, number of previous acute respiratory infection episodes and medical indications for influenza vaccination into account.

METHODS
Study design
A cohort study was conducted in a primary care population that represented the target group for influenza vaccination in 2019 in the Netherlands.

Setting and participants
The research focused on a large cohort of persons enlisted in general practices participating in Nivel Primary Care Database. This database is the largest one available in the Netherlands and it is used for national health and disease monitoring. To be included in the Nivel database, general practices needed to meet completeness and quality criteria. Therefore, sufficient data had to be provided on medical procedures, morbidity figures and prescriptions in 2018 and 2019. To ensure high recording quality, at least 70% of all morbidity data had to be provided with meaningful International Classification of Primary Care (ICPC) codes in correspondence with Dutch College for General Practitioners Clinical Standards (*Nederlands Huisartsen Genootschap Standaarden*) and which had been measured in ≥42 reporting weeks/year.[12] Only practices with complete data on influenza vaccinations were included, based on <10% difference between the number of recorded influenza vaccinations and number of claimed vaccines.[13]

Persons were included in a Nivel general practice throughout 2019 and belonged to the target group for the 2019/2020 influenza vaccination campaign in the Netherlands. This group included persons under 60 years of age with a medical indication for influenza vaccination and all persons aged 60 years and over.

Variables and data sources
Primary outcomes were time to general practitioner (GP)-diagnosed COVID-19 and time to all-cause mortality.

Next to the main independent variable, influenza vaccination in 2019, the following covariables were available: age, sex (male/female), comorbidities (cardiovascular diseases, pulmonary diseases, diabetes mellitus, impaired resistance to infections, chronic renal insufficiency, respiratory disorders due to neurological conditions and HIV) and the number of acute respiratory infection consultations in primary care (in 2019).

GP-diagnosed COVID-19 cases were reported from 10 March 2020, which corresponds to the time of notification of the first COVID-19 cases in the Netherlands, until 22 November 2020, when the statistical analyses started. GP-diagnosed COVID-19 was recorded for medically attended persons when (1) GPs diagnosed an acute infection of upper airways, other respiratory infections, influenza, pneumonia, other viral disease, other infectious disease, shortness of breath or coughing; and (2) recorded this as indicating a COVID-19 infection (whether or not test confirmed, also given circumstances such as test-confirmed COVID-19-positive housemates). Most cases had not been tested, as population-wide PCR testing was introduced in June 2020.

Mortality events were recorded throughout 2020 until 22 November 2020. Mortality labels were assigned to persons in our database when GPs recorded the ICPC code (A96) that corresponded with death, which was the best alternative for validated CBS (Statistics Netherlands) data that we were unable to incorporate in our database. Covariable information, such as presence of comorbidities, was obtained from patients' medical records at their GPs.

Bias
Confounding was reduced by adjusting for covariables with respect to demographic characteristics and specific (medical) indications for influenza vaccination. A randomised controlled trial would offer the highest methodological value. However, as it would be unethical to not vaccinate persons with the influenza vaccine proven to be effective in preventing influenza,[11] the best alternative was performed: a primary care population-based cohort study. Information bias was limited due to blinding of the researchers in terms of pseudonymisation of patients and general practices. Coding of variables was executed by Nivel investigators already before this study was set up.

Study size
Prior to the start of this study, it was calculated for different practical scenarios that the study size of our database would meet the study power (80%) requirements to detect a relative risk (RR) reduction of 25% for GP-diagnosed COVID-19 between influenza vaccinees and non-vaccinees (online supplemental parts I–III). A significance level of 0.05 was used in this study.

Statistical analysis and quantitative variables
Differences in numerical and categorical variables between the unvaccinated and vaccinated groups were

assessed using independent samples t-test and χ^2 test, respectively. Cox regression analyses were used to assess the effect of vaccination in 2019 on the time to GP-diagnosed COVID-19 and all-cause mortality. The following covariables were included in the models: age, sex (male/female), comorbidities and the number of acute respiratory infection consultations in primary care in 2019. For the all-cause mortality models, GP-diagnosed COVID-19 status (yes vs no) was also incorporated as a covariable. As all-cause mortality data collection started earlier than the recording of the first COVID-19 cases, models were adjusted for these time-to-event differences and the starting point was the same for GP-diagnosed COVID-19 cases and controls. In addition, an all-cause mortality analysis was performed for GP-diagnosed COVID-19 cases.

The linearity assumption was checked for numerical covariables. Due to a non-linear association with the outcomes and simplicity reasons, the numerical variable 'age' was divided into three age groups (0–59, 60–74, 75+ years) and included in the model. The same applied for 'acute respiratory infection consultations in 2019', where three groups were analysed (0, 1 and 2 or more consultations in 2019). In addition, proportional hazards assumptions were checked for all variables in the model via plotting of log-log (survival) curves and Schoenfeld residual testing. In case the proportional hazard assumption was violated, time-dependent covariables (interaction of a covariable with time) were computed and added to the proportional hazards (Cox regression) models. Covariables were removed via a top-down procedure if they did not contribute significantly to the model. Two-sided p values ≤0.05 were considered statistically significant. Multicollinearity was checked using variance inflation factors (VIF), where VIF≥10 indicates a (multi) collinearity problem.

Sensitivity analyses were performed to test the robustness of GP-diagnosed COVID-19 models and to exclude a potential effect by PCR testing which only became possible for the Dutch population after 1 June 2020. Therefore, two time periods were analysed separately, one representing the first COVID-19 wave (10 March to 1 June 2020) and the other representing the second wave (1 June to 22 November 2020) (online supplemental part IV). Since we were unable to use validated mortality data, mortality rates of our study were compared with those of the entire Dutch population (online supplemental part V). All analyses were performed using IBM SPSS Statistics for Windows (V.26.0, IBM). By reasons of large study groups which resulted in very small and non-informative p values, HRs with 95% CIs were assumed to be most useful and p values were omitted.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research.

Privacy and ethical considerations

The use of electronic health records for research purposes was allowed under certain conditions. When these conditions were fulfilled, neither obtaining informed consent from patients nor approval by a medical ethics committee was obligatory for this type of observational studies containing no directly identifiable data (Art 24 Dutch General Data Protection Regulation (GDPR) Implementation Act jo, Art 9.2 sub jGDPR).

Nivel received pseudonymised data from the participating general practices. After a second pseudonymisation for patients and general practices, data were transferred to this study's main researcher.[14]

RESULTS

For this study, data were available from 145 general practices, representing 223 580 enlisted persons with an indication for influenza vaccination. Numbers of outcome events and proportions to respective groups are presented in figure 1.

Descriptive data

Compared with the unvaccinated group, the vaccinated group was older (mean age±SD 67.0±15.2 vs 60.6±16.1), represented relatively more females (53.7% vs 50.1%),
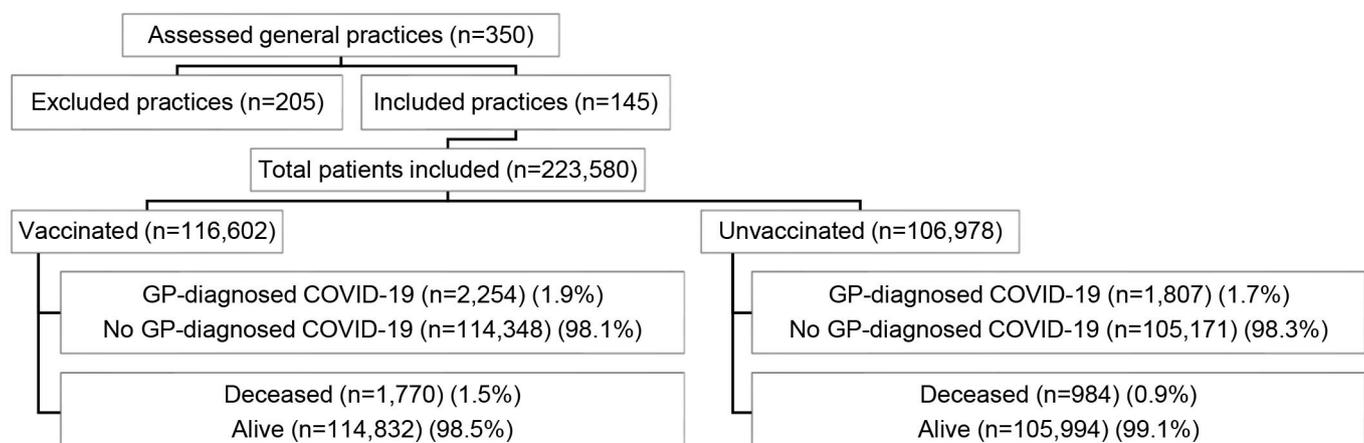

Figure 1 Total number of persons, by GP-diagnosed COVID-19 status and by all-cause mortality. GP, general practitioner.

Table 1 Study population: baseline characteristics

Patient characteristic	Unvaccinated n (% of total group of 106 978)	Vaccinated n (% of total group of 116 602)	P value (χ^2)
Age group (years)			<0.001
0–59	31 796 (29.7)	24 406 (20.9)	
60–74	60 857 (56.9)	55 992 (48.0)	
75+	14 325 (13.4)	36 204 (31.0)	
Sex, female	53 571 (50.1)	62 590 (53.7)	<0.001
Cardiovascular disease	16 253 (15.2)	27 345 (23.5)	<0.001
Pulmonary disease	17 591 (16.4)	18 942 (16.2)	0.205
Diabetes mellitus	15 376 (14.4)	24 095 (20.7)	<0.001
Impaired resistance to infections	7348 (6.9)	6566 (5.6)	<0.001
Chronic renal insufficiency	3845 (3.6)	6599 (5.7)	<0.001
Respiratory disorder by neurological conditions	4929 (4.6)	6268 (5.4)	<0.010
HIV	214 (0.2)	179 (0.2)	<0.001
Number of acute respiratory infection consultations in 2019			<0.001
0	96 794 (90.5)	100 682 (86.3)	
1	6363 (5.9)	9294 (8.0)	
≥2	3821 (3.6)	6626 (5.7)	

had more often comorbidities and had relatively more acute respiratory infection consultations in 2019 (table 1).

Main results
GP-diagnosed COVID-19
It was found that there was a slightly positive association between influenza vaccination in 2019 and COVID-19 rates (HR 1.15; 95% CI 1.08 to 1.22) (table 2). GP-diagnosed COVID-19 rates were higher for females, for persons with cardiovascular disease, pulmonary disease, diabetes mellitus or chronic renal insufficiency and for persons with one or more GP visits for acute respiratory infections in 2019, and lower for older age groups (≥60 years compared with <60 years) (table 2).

All-cause mortality
Regarding all-cause mortality rates, a slightly protective effect was found for influenza vaccination (HR 0.90; 95% CI 0.83 to 0.97) (table 3). Higher all-cause mortality rates were found for older age groups, males and for persons with GP-diagnosed COVID-19, cardiovascular disease, pulmonary disease, diabetes mellitus, impaired resistance to infections, chronic renal insufficiency, respiratory disorder by neurological conditions or those with one or more GP visits for acute respiratory infections in 2019 (table 3).

All-cause mortality, subanalysis for GP-diagnosed COVID-19 persons
Specifically, for GP-diagnosed COVID-19 persons, no significant association was found between influenza vaccination and all-cause mortality rates, and outcomes for

other covariables were comparable to those in the total group of persons in this study (tables 3 and 4).

Sensitivity analyses
Sensitivity analyses showed that associations between influenza vaccination and GP-diagnosed COVID-19 rates were consistent over time, as shown by the models for the first and second COVID-19 waves, respectively (online supplemental part IV). All-cause mortality numbers from our study population were similar to those of the total Dutch population and also when different age groups and sexes were compared (online supplemental part V).[15]

DISCUSSION
Key findings
In this primary care cohort study among 223 580 persons from the target group for influenza vaccination in 2019 in the Netherlands, a slightly positive association was found between influenza vaccination in 2019 and GP-diagnosed COVID-19 rates in 2020 (HR 1.15; 95% CI 1.08 to 1.22). We also observed a slightly negative association between influenza vaccination and all-cause mortality rates (HR 0.90; 95% CI 0.83 to 0.97). For the group GP-diagnosed COVID-19 cases, no significant association was found between influenza vaccination in 2019 and all-cause mortality rates.

Strengths and limitations
Important strengths of this study were using a representative sample of the Dutch target group for influenza

Table 2 HRs for GP-diagnosed COVID-19, adjusted for covariables, total group (n=223 580)

Covariable	GP-diagnosed COVID-19 HR	95% CI
Influenza vaccination in 2019 (yes vs no)	1.15	1.08 to 1.22
Age group, relative to group 0–59 years		
60–74 years	0.68	0.63 to 0.73
75+ years	0.67	0.61 to 0.73
Sex (female vs male)	1.08	1.02 to 1.15
Cardiovascular disease (yes vs no)	1.11	1.03 to 1.20
Pulmonary disease (yes vs no)	1.15	1.06 to 1.25
Diabetes mellitus (yes vs no)	1.30	1.21 to 1.40
Chronic renal insufficiency (yes vs no)	1.19	1.04 to 1.37
Number of acute respiratory infection consultations in 2019, relative to 0		
1	1.28	1.15 to 1.43
≥2	1.50	1.33 to 1.69

GP, general practitioner.

Table 3 Adjusted HRs for all-cause mortality and its covariables, total group (n=223 580)

Covariable	All-cause mortality HR	95% CI
Influenza vaccination in 2019 (yes vs no)	0.90	0.83 to 0.97
Age group, relative to group 0–59 years		
60–74 years	2.90	2.45 to 3.42
75+ years	11.00	9.35 to 12.95
Sex (female vs male)	0.82	0.76 to 0.89
GP-diagnosed COVID-19 (yes vs no)	10.90	8.51 to 13.96
Cardiovascular disease (yes vs no)	1.76	1.62 to 1.91
Pulmonary disease (yes vs no)	1.96	1.80 to 2.14
Diabetes mellitus (yes vs no)	1.54	1.41 to 1.67
Impaired resistance to infections (yes vs no)	2.24	1.98 to 2.53
Chronic renal insufficiency (yes vs no)	1.87	1.67 to 2.07
Respiratory disorders by neurological conditions (yes vs no)	1.77	1.58 to 2.00
Number of acute respiratory infection consultations in 2019, relative to 0		
1	1.25	1.10 to 1.42
≥2	1.62	1.43 to 1.84

GP, general practitioner.

vaccination, the primary care population-based cohort design, adjustments for relevant covariables and sensitivity analyses. But there were also several limitations. First, there is a possibility of residual confounding by risk factors that could not be evaluated in this study. Literature suggests that such COVID-19 risk factors could be high population density,[16] low socioeconomic status accompanied by a possible lack of health-seeking behaviour and insufficient health resources,[17 18] belonging to ethnic minorities,[16 18–21] being a healthcare worker[16 19 22] or low compliance to COVID-19 regulations (eg, difficulties keeping 1.5 m distance because of mental disorders[23] or scepticism on COVID-19 existence), high Clinical Frailty Scale scores,[24] unhealthy behaviour such as smoking[25 26] and high body mass index, especially in combination with low physical activity.[27 28] These factors could have been differently distributed between vaccinated and unvaccinated groups.

Additionally, misclassification could induce information bias because PCR testing options were limited during the first wave. However, our sensitivity analyses found consistent associations between influenza vaccination and GP-diagnosed COVID-19 for the first wave and the second wave (when nationwide PCR testing was available free of charge) (online supplemental part IV) and COVID-19 incidences were similar between our population and total

population data.[29] All-cause mortality rates were similar in our study population and the general population (online supplemental table SV-1), even though we used ICPC recordings instead of mortality data validated by Statistics Netherlands (CBS). Interestingly, the General Practice Research Consortium Netherlands described under-reporting of COVID-19-related deaths because of a low SARS-CoV-2 testing capacity in the first wave of the pandemic, based on a national registration study.[30] However, there is no reason to assume that either misclassification or under-reporting would lead to more missed cases for either unvaccinated or vaccinated groups, and sensitivity analyses indicated the robustness of models as well.

Interpretation
Influenza vaccination and GP-diagnosed COVID-19 rates
The slightly positive association between influenza vaccination and GP-diagnosed COVID-19 was not found in other observational studies. In a cohort of 27 201 patients with a laboratory SARS-CoV-2 test within the Michigan

Table 4 Adjusted HRs for all-cause mortality and its covariables, subanalysis COVID-19 group (n=4061)

Covariable	All-cause mortality HR	95% CI
Influenza vaccination in 2019 (yes vs no)*	1.12	0.77 to 1.62
Age group, relative to group 0–59 years		
60–74 years	5.54	2.35 to 13.06
75+ years	23.75	10.26 to 54.97
Sex (female vs male)	0.66	0.48 to 0.91
Cardiovascular disease (yes vs no)	1.88	1.35 to 2.62
Diabetes mellitus (yes vs no)	1.87	1.35 to 2.59
Impaired resistance to infections (yes vs no)	1.84	1.09 to 3.10

*Presented in table as it contributes to answering the main research question despite an insignificant association.

healthcare system, influenza vaccination was protective against COVID-19 (0.76; 95% CI 0.68 to 0.86).[31] A similar association was also found in an Italian case-negative study (OR 0.89; 95% CI 0.80 to 0.99)[32] and a Spanish cohort with patients from both nursing homes and primary care centres (HR 0.63; 95% CI 0.44 to 0.91).[33] A large multicentre primary care study in five European countries found no significant association (OR 0.93; 95% CI 0.66 to 1.32) in a case–control design.[34] As we previously discussed, the slight effects that we found may have been caused by residual confounding factors that we could not adjust for, such as socioeconomic and behavioural circumstances, and the use of clinical diagnoses instead of test-confirmed cases. However, also other observational studies are confronted with residual confounding. Moreover, differences between study designs and study populations may be an explanation for the differences in study results. As said before, in contrast to other studies, our study is a primary care population-based cohort study regarding the influenza vaccination target group.

Similar to our study, other research also found positive associations between comorbidities and COVID-19 incidences.[25 31 33 35–37] Comorbidities were more present among the vaccinated group in our study, who therefore may require more assistance in everyday tasks and may live together with more individuals per household, indirectly making them more at risk for COVID-19 transmission. Studies showed that nursing home residence was a predisposing factor for COVID-19,[33] and comorbidities were associated with poorer clinical outcomes among COVID-19 cases.[38] Health-seeking behaviour could have played a role and is known to be more frequent among women with influenza-like illness,[39] which was more found among the vaccinated group. For these reasons,

models were adjusted by different covariables including age, sex and comorbidities.

Influenza vaccination and all-cause mortality rates

GP-diagnosed COVID-19 was strongly associated with all-cause mortality rates (HR 10.90; 95% CI 8.51 to 13.96), which was also found in another population-based cohort study.[40] Although we did not have access to COVID-19-associated mortality data in our study, other research showed that COVID-19 mortality risks were lower after influenza vaccination.[9 41 42] Possibly, influenza vaccinations have a wider beneficial impact on health, such as on cardiometabolic diseases, which are associated with COVID-19 hospitalisation or death.[43–47] Furthermore, it may protect against other viral respiratory infections[2 3 10] which are risk factors[48] for the leading global cause of death: cardiovascular diseases.[49]

An overall health benefit is plausible as other death causes most likely did not differ between influenza vaccinees and non-vaccinees throughout 2020, such as traffic incidents and natural disasters. The quality of the influenza vaccine was considered good, as circulating influenza subtypes were similar to the strains in the quadrivalent vaccine,[50–52] resulting in a mild and short 2019 influenza epidemic in the Netherlands.[51 52] Next to the associations we found between influenza vaccination, COVID-19 and all-cause mortality rates and considering that we did not have access to data on different causes of mortality, it is also interesting to elaborate on severe COVID-19 disease in other literature. In a population of patients positive for COVID-19, it was found that severe outcomes were more likely for those who were not vaccinated against influenza, specifically sepsis (RR 1.36–1.45, where RRs were measured 1–4 months after COVID-19 diagnosis), stroke (RR 1.45–1.58), intensive care unit (ICU) admissions (RR 1.17–1.20), deep venous thrombosis events (RR 1.41–1.53) and emergency department visits (RR 1.20–1.58).[53] In American studies, influenza vaccination protected against hospitalisation (OR 0.58; 95% CI 0.46 to 0.73),[31] resulted in shorter hospital stays (OR 0.76; 95% CI 0.65 to 0.89)[31] and reduced the number of ICU admissions.[54] Protective effects were also found in a study with test-positive patients with COVID-19 only whereas patients who were not vaccinated against influenza had higher odds to be hospitalised (OR 2.44; 95% CI 1.68 to 3.61) or to be admitted to ICUs (OR 3.29; 95% CI 1.18 to 13.77).[55] In a case–control study, however, no significant association was found between influenza vaccination and hospitalisation (OR 1.00; 95% CI 0.84 to 1.29) or mortality (HR 1.14; 95% CI 0.95 to 1.37) in patients with COVID-19.[32]

Lastly, in our study, being female was associated with lower all-cause mortality rates (OR 0.82; 95% CI 0.76 to 0.89). Mortality data validated by CBS (Statistics Netherlands) also showed that all-cause mortality rates were higher for males (online supplemental part V).[15] Considering international data from 1 million excess deaths in 29 high-income countries, age-standardised excess death

rates in 2020 were higher in men compared with women.[56] International studies on severe course of COVID-19, including systematic reviews and meta-analyses, also found higher mortality risks for older age as well as for males.[26 40 57–66]

Generalisability

In a broader context than our study setting, these recent findings are representative for the target group influenza vaccination in the Netherlands. We made use of the largest national health monitoring source for infectious disease data, which met high completeness and quality criteria. This resulted in a considerable number of patients (n=223 580) and associations remained consistent in sensitivity analyses.

Since there are differences in the findings of international studies on the impact of influenza vaccination on COVID-19 incidences, also given the limitations of the various studies, further studies should evaluate these findings. On an immunological level, it is interesting to further investigate to what extent influenza vaccinations trigger trained immunity against other pathogens, and in particular if immunological memory is stimulated, which is known to persist for at least 6–8 months among around 90% from those with a previous COVID-19 infection.[67]

CONCLUSION

Our study findings contribute to the knowledge about the impact of influenza vaccination on other respiratory illnesses. Our hypothesis of a possible negative association between influenza vaccination in 2019 and GP-diagnosed COVID-19 rates was not confirmed, as we found a slightly positive association. A slightly protective effect on all-cause mortality was found after influenza vaccination, possibly by a wider, overall protective effect on health. Future research designs should include test-confirmed COVID-19 cases and controls, adjustments for behavioural, socioeconomic and ethnic factors and validated disease-specific mortality causes.

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SUPPLEMENTARY DATA

Part I – Power calculation summary for different scenarios

In the earliest stage of this research, power size calculations were performed, and it was evident the Nivel database would best suit our study purposes. Nivel systematically tracks the Dutch health system and report sudden changes in disease patterns, for which it weekly collects –anonymized– data from 350 'surveillance' general practices in the Netherlands. Nivel monitors incidence of different types of diseases, such as circulation of infectious diseases. For patients that were subscribed to participating general practices in the Nivel surveillance system, medical records were tracked, such as previous diagnoses and classifications used for symptoms associated with COVID-19. For a subgroup of 40 'sentinel' stations (that belonged to the total group of 350 general practices), PCR-COVID-19-tests were taken, and it was investigated which group would meet this study's power (80%) requirements, as described below.

Power calculations

In the period from 10 March to 22 November 2020, Nivel reported that Dutch general practitioners recorded over 123,000 GP-diagnosed COVID-19 patients during COVID-19 pandemic. On the basis of these data and the further expected course, it was estimated that in the Nivel practices, in the period from 10 March to the start of this statistical analyses (22 November 2020), there would be more than sufficient cases to detect a relative risk reduction of 25% after influenza vaccination for patients with GP-diagnosed COVID-19, applying an alpha of 0.05 and a power of 0.80 in two-tailed testing (SPSS version 26.0, Armonk, NY: IBM Corp.). We aimed for a 25% risk reduction for GP-diagnosed COVID-19 after influenza vaccination, after a recent study had shown a risk reduction of 39% (p=0,001) on COVID-19 incidence for those had received influenza vaccination during the 2019/2020 winter season, compared to those who had not received it.(1) This was done in a study population of 10631 Dutch hospital employees with a lower age (average age of 41 years for the COVID-19 positive group and 42 years for the COVID-19 negative group).(1)

We executed power calculations for different scenarios to explore which subjects should be included in this study [Supplementary part II].

Table SI-1 Power calculations for study population scenarios.

Scenario	Inclusion	Power
A	Nivel40, COVID-19 test-positive patients only	49.4%
B	Nivel40, COVID-19 test-positive and suspected patients	96.3%
C	Nivel350, COVID-19 test-positive patients only	99.1%
D	Nivel350, COVID-19 test-positive and suspected patients	100%
E	Nivel350, COVID-19 test-positive patients aged 60 years and older	97.7%
F	Nivel350, COVID-19 test-positive and suspected patients aged 60 years and older	100%

For all scenarios, two-sided testing was used, with alpha 0.05, beta 0.20 and a 25% relative risk reduction for GP-diagnosed COVID-19 to be minimally detected.

It was concluded that for the data from 350 Nivel surveillance stations, a high power would be achieved, either for the test-positive patients only, or for a combination of COVID-19 test-positive patients and GP-diagnosed COVID-19 patients. For the subgroup of patients aged 60 years and older, a high power would be achieved as well. For the 40 Nivel Sentinel stations, a high power could be achieved when including both test-positive and suspected patients. Using the Nivel350 group was therefore the safest option to reach sufficient study power.

Part II – Elaboration of different scenarios

In this section, the power calculations are described for different scenarios and which were executed prior to the retrieval of the database in November 2020. In all scenarios, group 1 corresponds with the group that was vaccinated against the influenzavirus. Group 2 corresponds with the unvaccinated group. To reach a relative risk reduction of at least 25%, the incidence of group 1 is 75% of group 2 (base population). For the power calculations as described below, which were done in July 2020, it was assumed that there were no proportional differences in GP-diagnosed COVID-19 incidence between unvaccinated and vaccinated groups between the situation in July 2020 and that in November 2020.
The following data were accessed when the study protocol was written, on 21 July 2020:
a.   COVID-19 cases till 21 July 2020 (total population of 17.28 million inhabitants)
-     GP-diagnosed COVID-19 =   123,500 = 0.7147% (of 17.28 million) (2, 3)
-     Test-confirmed COVID-19 cases: 52,073 = 0.3013%   (4)
  -     50% aged ≥ 60 years   26,036
-     Hospitalized   11,902   (4)
  -     70% aged ≥ 60 years   8,331
-     Died (positively tested)   6,136   (4)
  -     97% aged ≥ 60 years   5,952

b.   Vaccinated group:
-     18% (= 3.1 million)   (5)
  -     At-risk group = 50%   (5)
  -     All aged ≥60 years old = 55%   (5)
  -     4.44 million persons that represent 25.7% of the Dutch population: 0.55x4.44 = 2.4 million vaccinated persons aged 60 years or above   (2)

'Nivel350' (representing 350 surveillance family care practices)
-     Base population: 1.3 million (approximately 8% of the total Dutch population)

'Nivel40' (representing 40 Sentinel stations)
-     Base population: 130,000 (approximately 8% of the total Dutch population)
  -     Including those aged ≥60 years: 34,560
-     18% vaccinated against influenza   23,400
  -     Including those aged ≥60 years: 0.55x34,560   19,008
-     Total number of unvaccinated: 130,000–23,400=106,600
-     GP-diagnosed COVID-19   929   (0.7147% of 130,000)
-     Test-confirmed COVID-19   392   (0.3013% of 130,000)
  -     aged ≥60 years (50%):   181/34,560 x 100% = 0.524%
-     Suspected plus test-confirmed cases: 1321   (1.0160% of 130,000)
  -     aged ≥60 years (50%):   6,601/34,560 x 100% = 19.1%
-     Hospitalized: 96   (0.074%)
-     Died (test-confirmed COVID-19 cases):   48   (0.037%)

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For the power calculations, *Clin Calc* software was used.(6)
- An alpha of 0.05 was used to detect significant risk reductions of at least 25%.
- Assumptions: for the unvaccinated group, the cumulative incidence is the incidence of the base population. The incidence of group 1 (vaccinated) is 75% of the incidence of group 2 (unvaccinated).
- Prior to the power calculations, predictions were made (in July 2020) for the number of cases in November 2020 and which are described in Supplementary Part III.

Scenario A. 'Nivel40': test-confirmed COVID-19 cases
Number of cases till July 2020: 360 (base incidence: 0.3013%)   (3)

Table SII-1 Power calculation outcomes scenario A.

Post-hoc Power	
49.4%	
Study Parameters	
Incidence, group 1	0.2260%
Incidence, group 2	0.3013%
Subjects, group 1	23400
Subjects, group 2	106600
Alpha	0.05

Note. Dichotomous endpoint, two Independent Samples Study.

Scenario B. 'Nivel40': test-confirmed COVID-19 cases and GP-diagnosed COVID-19 cases
Number of cases till July 2020: 1321 (base incidence: 1.0160%)   (3)

Table SII-2 Power calculation outcomes scenario B.

Post-hoc Power	
96.3%	
Study Parameters	
Incidence, group 1	0.762%
Incidence, group 2	1.0160%
Subjects, group 1	23400
Subjects, group 2	106600
Alpha	0.05

Note. Dichotomous endpoint, two Independent Samples Study.

Scenario C. 'Nivel350': test-confirmed COVID-19 cases
- Prediction of number of COVID-19 test-confirmed cases in week 47: 2.59% / 100% x 67,625 = 1.751 (3).
- Predicted base population: 0.0259 x 17.28 million = 447,500   (2,3)
  - Therefore, the incidence is 1,751/447,500 = 0.0039128.
- Vaccinated: 18% x 447,500   =   80,550   (2,5)
- Unvaccinated: 82% x 447,500   =   366,950   (2,5)

Table SII-3 Power calculation outcomes scenario C.

Post-hoc Power	
99.1%	
Study Parameters	
Incidence, group 1	0.29346%
Incidence, group 2	0.39128%
Subjects, group 1	80550
Subjects, group 2	366950
Alpha	0.05

Note. Dichotomous endpoint, two Independent Samples Study.

Scenario D. 'Nivel350': test-confirmed COVID-19 cases and GP-diagnosed COVID-19 cases
- Prediction of number of GP-diagnosed COVID-19 cases during COVID-19 pandemic in week 47: 2.59% / 100% x 170,156 = 4,407 (3).
- Therefore, the incidence of test-confirmed COVID-19 cases plus GP-diagnosed COVID-19 cases = (1,751 + 4,407) / 447,500 = 0.01376089 = 1.376089%.
  - P1 is 75% (based on expected risk reduction of 25%): 1.032067%.
- Vaccinated: 18% x 447,500   =   80,550   (2,5)
- Unvaccinated: 82% x 447,500   =   366,950   (2,5)

Table SII-4 Power calculation outcomes scenario D.

Post-hoc Power	
100%	
Study Parameters	
Incidence, group 1	1.032067%
Incidence, group 2	1.376089%
Subjects, group 1	80550
Subjects, group 2	366950
Alpha	0.05

Note. Dichotomous endpoint, two Independent Samples Study.

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<u>Scenario E. 'Nivel350': test-confirmed COVID-19 cases, group ≥60 years old</u>
The group ≥ 60 years old represents 25.671% of the total Dutch population.(1) On average, 55% gets vaccinated against influenza.(5)
- N1 = number of vaccinated individuals aged ≥ 60 years:
0.25671 x 447,500 x 0.55 = 63,180
- N2 = number of unvaccinated indivduals aged ≥ 60 years:
0.25671 x 447,500 x 0.45 = 51,690
- N1 + N2 = 114,870
- 50% of 1751 test-confirmed cases = 876
  o 876 / 114,870 = 0.0076260 (p2; base incidence)
    • p1 = 75% = 0.0057195

Table SII-5 Power calculation outcomes scenario E.

Post-hoc Power	
97.7%	
Study Parameters	
Incidence, group 1	0.57195%
Incidence, group 2	0.76260%
Subjects, group 1	63180
Subjects, group 2	51690
Alpha	0.05

Note. Dichotomous endpoint, two Independent Samples Study.

<u>Scenario F. 'Nivel350': test-confirmed COVID-19 cases and GP-diagnosed COVID-19 cases, group ≥60 years old</u>
- 50% of test-confirmed and GP-diagnosed COVID-19 (1,751 + 4,407) = 3,079
  o 3,079 / 114,870 = 0.0268042 (p2; base incidence)
    • p1 = 75% = 0.02010316

Table SII-6 Power calculation outcomes scenario F.

Post-hoc Power	
100%	
Study Parameters	
Incidence, group 1	2.01032%
Incidence, group 2	2.68042%
Subjects, group 1	63180
Subjects, group 2	51690
Alpha	0.05

Note. Dichotomous endpoint, two Independent Samples Study.

Part III – Assumptions for power calculations

Predictions were made for the total number of COVID-19 cases in week 47 (when the analyses started) and which was based on the Nivel data which were accessible on 21 July 2020.(3) The numbers on July 21st were retrieved from the data from 350 general practices.(3) Every week, these practices provide epidemiological data for various conditions, and which are used by Nivel to monitor the incidence of certain diseases in the total population, such as infectious diseases.(5) This surveillance system is also used to monitor the COVID-19 situation in the Netherlands.(3-5)

Number of confirmed and suspected COVID-19 cases in the period from 10 March 2020 (week 10) up to and included week 29 in 2020 (which is the moment of the power calculations):

- 52,073 confirmed COVID-19 cases (on 21 July 2020);(3)
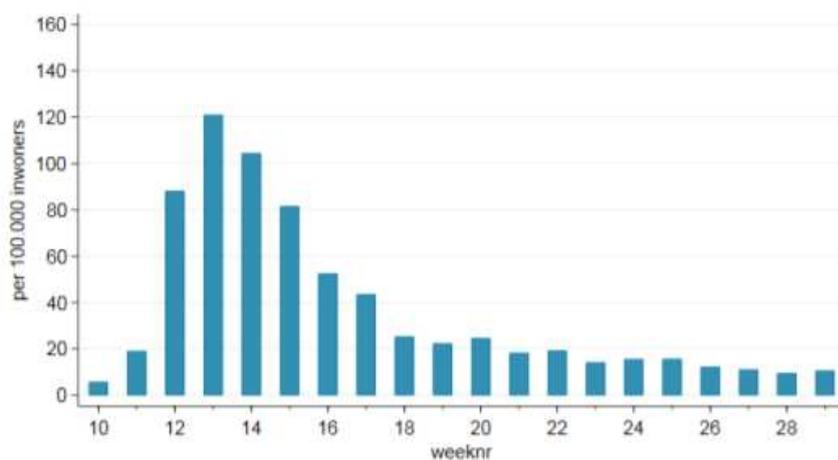- 123,500 COVID-19 suspected COVID-19 cases (on 21 July 2020).(3)

Figure SIII-1 Total number of patients with a first contact GP-visit because of COVID-19 related symptoms (excluding test-confirmed COVID-19), per 100,000 inhabitants.(3)
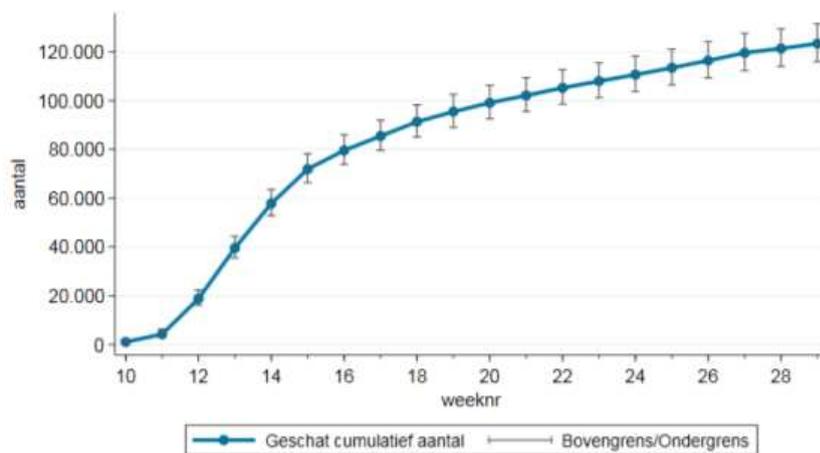

Figure SIII-2 Total number of patients with a first contact GP-visit because of COVID-19 related symptoms (excluding test-confirmed COVID-19), up to and included week 29 in 2020 (in the Netherlands) (including 95% confidence intervals).(3)

Assumptions and prediction of COVID-19 cases in week 47 (2020)
From week 47 in 2020, the analyses started. The number of COVID-19 cases were predicted, based on the available data in week 28 (2020).(3) The following was assumed for the time between period 28 up to and including week 47:
1.   Every week, there will be added at least 5 new test-confirmed COVID19 cases (per 100,000 inhabitants);
2.   Every week, there will be at least 15 GP-diagnosed COVID-19 cases during the COVID-19 pandemic (per 100,000 inhabitants).

Total Dutch population: estimated number of COVID-19 test-confirmed cases in week 47: 52,073 + ((5/100,000) x 17,280,000 x 18 weeks) = 67,625.
Total Dutch population: estimated number of - GP-diagnosed COVID-19 cases in week 47: 123,500 + ((15/100,000) x 17,280,000 x 18 weeks) = 170,156.
Estimation of total amount of COVID-19 cases (test-confirmed and GP-diagnosed COVID-19 cases) in the Nivel surveillance practices
Based on the *Monitor Vaccinatiegraad Nationaal Programma Grieppreventie 2018* (5), 163/440 general practices (37%) were included in the 2018 Nivel analyses. Inclusion criteria were based on the availability and quality of data as provided by the practices and which are available to the Stichting Nationaal Programma Grieppreventie (SNPG) for a >90% similarity between registered and declared vaccinations. In the Netherlands, there are approximately 5020 family care practices [5]. For 350 of them (the Nivel surveillance stations), there is provided weekly data, which are used by Nivel for their analyses. Taking into account the fraction 37% which was included in the Nivel database, it is expected that 130 practices are included for the 2019 Nivel analyses, and therefore, for this study.
Proportion Nivel practices, relative to total number of general practices in the Netherlands = 130/5,020 = 2.59%
Nivel surveillance practices: expected number of test-confirmed COVID-19 cases in week 47: 2.59% / 100% x 67,625 = 1,751
Nivel surveillance practices: expected number of GP-diagnosed COVID-19 cases during COVID-19 pandemic in week 47: 2.59% / 100% x 171,800 = 4,407
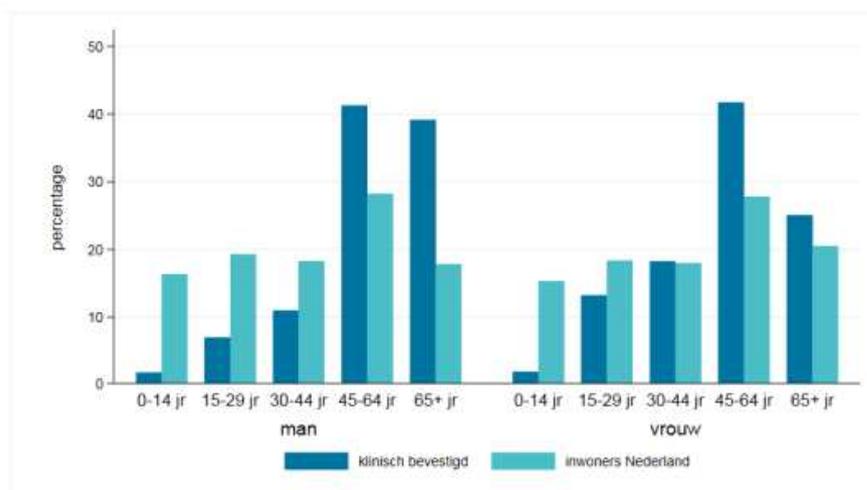

Figure SIII-3 Estimation of the percentage GP-diagnosed COVID-19 (in the Netherlands) for males and females, and the percentage distribution for the number of inhabitants in the Netherlands, per age group (week 10-21 2020).(3)

Part IV: Sensitivity Analyses

FIRST WAVE – GP-DIAGNOSED COVID-19

Table SIV-1 Hazard Ratios for GP-diagnosed COVID-19, adjusted for covariables, 10 March – 1 June 2020 (first wave) (n=223,580).

Covariable	GP-diagnosed COVID-19 Hazard Ratio	95% Confidence Interval
Influenza vaccination in 2019 (yes vs no)	1.19	1.04 – 1.36
Age group, relative to group 0-59 years		
60-74 years	0.97	0.82 – 1.15
75+ years	1.36	1.13 – 1.64
Cardiovascular disease (yes vs no)	1.27	1.09 – 1.47
Pulmonary disease (yes vs no)	1.38	1.17 – 1.62
Diabetes mellitus (yes vs no)	1.47	1.26 – 1.70
Impaired resistance to infections (yes vs no)	1.41	1.12 – 1.79
Chronic renal insufficiency (yes vs no)	1.39	1.09 – 1.77
Respiratory disorders by neurological conditions (yes vs no)	1.52	1.20 – 1.92
Number of acute respiratory infection consultations in 2019, relative to 0		
1	1.40	1.13 – 1.74
≥2	1.55	1.22 – 1.98

SECOND WAVE – GP-DIAGNOSED COVID-19

Table SIV-2 Hazard Ratios for GP-diagnosed COVID-19, adjusted for covariables, 1 June – 22 November 2020 (second wave) (n=222,580).

Covariable	GP-diagnosed COVID-19 Hazard Ratio	95% Confidence Interval
Influenza vaccination in 2019 (yes vs no)	1.13	1.05 – 1.22
Sex (female vs male)	1.09	1.02 – 1.17
Age group, relative to group 0-59 years		
60-74 years	0.60	0.56 – 0.65
75+ years	0.53	0.48 – 0.59
Diabetes mellitus (yes vs no)	1.24	1.13 – 1.35
Respiratory disorders by neurological conditions (yes vs no)	0.79	0.66 – 0.95
Number of acute respiratory infection consultations in 2019, relative to 0		
1	1.25	1.11 – 1.42
≥2	1.50	1.30 – 1.72

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Part V: Mortality rates comparison between national data and data of this study

Table SV-1 Comparison of mortality rates between total population data and the primary care population-based cohort.

	Total population	Our data
Total group (males and females)		
65-79 years old	1.43%	1.08%
80+ years old	8.28%	4.82%
Males		
65-79 years old	1.73%	1.30%
80+ years old	9.21%	5.66%
Females		
65-79 years old	1.15%	0.87%
80+ years old	7.69%	4.25%

Note. This study was a primary care population-based cohort. Total population data from CBS included persons that were admitted in hospitals and nursing-home residences(7) and these persons were not part of our population.

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