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## Original Research

## No increased incidence of venous thrombosis or pulmonary embolism after SARS-CoV-2 vaccination in Germany

C. Tanislav<sup>a,\*</sup>, J. Rosenbauer<sup>a</sup>, R. Zingel<sup>b,c</sup>, K. Kostev<sup>b</sup><sup>a</sup> Department of Geriatrics and Neurology, Diakonie Hospital Jung Stilling, Siegen, Germany<sup>b</sup> Epidemiology, IQVIA, Frankfurt Am Main, Germany<sup>c</sup> Centre of Excellence Vaccine, IQVIA, Frankfurt Am Main, Germany

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## ABSTRACT

**Objectives:** Vaccination is one of the most effective measures to combat the COVID-19 pandemic. The main reason for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination hesitancy is the potential side-effects. This study aimed to investigate the incidence of venous thrombosis and pulmonary embolism in patients who received SARS-CoV-2 vaccination.

**Study design:** This was a retrospective cohort study.

**Methods:** Individuals aged  $\geq 18$  years who received an initial vaccination for COVID-19 in one of 1134 general practices in Germany between April and June 2021 were included in the study. Vaccinated patients were matched to unvaccinated individuals by age, sex, index month (April to June 2020 [unvaccinated cohort] or April to June 2021 [vaccinated cohort]) and diagnoses that may be associated with an increased incidence of thrombosis documented within 12 months before the index date. The incidences of thrombosis and non-fatal pulmonary embolism as a function of COVID-19 vaccination were analysed.

**Results:** The present study included 326,833 individuals who were vaccinated against COVID-19 and 326,833 matched unvaccinated individuals. During the follow-up period, 406 vaccinated patients and 342 individuals in the control group received a diagnosis of thrombosis or non-fatal pulmonary embolism. This resulted in an incidence rate of 11.9 vs 11.3 cases per 1000 patient-years for vaccinated vs unvaccinated individuals, respectively, and a non-significant overall incidence rate ratio (IRR: 1.06; 95% confidence interval [CI]: 0.93–1.22). The highest IRR was observed in the 41–60 years age group (IRR: 1.30; 95% CI: 0.98–1.73), and the lowest IRR was seen in the 18–40 years age group (IRR: 0.6; 95% CI: 0.0–1.05); however, none of the individual age group incidence rates was significant.

**Conclusions:** The results indicate that the occurrence of thrombosis or pulmonary embolism after COVID-19 vaccination is a coincidental finding rather than a consequence of vaccination.

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## Introduction

The COVID-19 pandemic has had a dramatic impact worldwide, affecting both social lives and economic development.<sup>1–5</sup> The use of the recently developed vaccines has proven effective in combating the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and preventing severe outcomes of COVID-19.<sup>6</sup> However, vaccine hesitancy has been reported in many countries for a variety of reasons.<sup>7</sup> Although vaccine rollouts have increased

over time, vaccination hesitancy has remained an issue.<sup>7,8</sup> In addition to an obvious gap in vaccination rates between developed and developing countries, a similar trend has emerged regarding vaccine hesitancy, with factors such as higher education level, higher income, non-rural residency and free vaccination provision being identified as determinants for vaccine acceptance.<sup>7,8</sup> Some investigations have indicated that a general trust in authorities and the government correlates strongly with willingness to be vaccinated.<sup>7</sup> However, potential vaccine side-effects have been identified as the most common reason for COVID-19 vaccine hesitancy and were cited by more than 90% of the vaccine-hesitant individuals questioned.<sup>8,9</sup> Common postvaccination side-effects, such as local reactions, fever, fatigue, headache or joint pain, are of minor relevance and are non-life threatening.<sup>10</sup> On the other hand, some

\* Corresponding author. Department of Geriatrics and Neurology, Diakonie Hospital Jung Stilling, Wichernstrasse 40, 57074 Siegen, Germany. Tel.: +49 271333340353.

E-mail address: [christian.tanislav@diakonie-sw.de](mailto:christian.tanislav@diakonie-sw.de) (C. Tanislav).

events, such as autoimmune inflammatory neurological or vascular and haematological disorders, including myocardial infarction, thrombosis, cerebral vein thrombosis and thrombocytopenia, have been identified as having a potential association with the vaccine (11–15). However, reports of these types of serious adverse events in the literature are rare, and their link to COVID-19 vaccination remains a topic of discussion.<sup>16</sup> In the context of vaccine hesitancy and the global COVID-19 pandemic, it is important to investigate the incidence of such events using robust data, for example, data derived from large-scale investigations. Providing reliable evidence of the safety of COVID-19 vaccines may help to boost confidence and improve acceptance of these recently developed vaccines.

Therefore, this study investigated the frequency of thrombosis and non-fatal pulmonary embolism in patients who received the SARS-CoV-2 vaccine. Data were obtained from a large database that is supplied with information from general practitioners (GPs) and specialists in Germany.

## Methods

### Database

This study used data from the Disease Analyzer database (IQVIA), which contains drug prescriptions, diagnoses and basic medical and demographic information that is obtained directly and in an anonymous format from computer systems used in the practices of GPs and specialists.<sup>17</sup> The database covers approximately 3% of all outpatient practices in Germany. Diagnoses (according to International Classification of Diseases, 10th revision [ICD-10]), prescriptions (according to Anatomical Therapeutic Chemical classification system) and the quality of the reported data are monitored regularly by IQVIA. In Germany, the sampling methods used to select physicians' practices are appropriate for obtaining a representative database of general and specialised practices. It has previously been shown that the panel of practices included in the Disease Analyzer database is representative of general and specialised practices in Germany.<sup>17</sup> In addition, this database has already been used in previous studies focusing on COVID-19<sup>18,19</sup> as well as cardiovascular outcomes.<sup>20,21</sup>

### Study population

This retrospective cohort study included individuals aged  $\geq 18$  years who received a COVID-19 vaccination in one of 1134 general practices in Germany between April and June 2021 (index date; Fig. 1). Individuals with thrombosis (ICD-10: I80–I82) or pulmonary embolism (ICD-10: I26) diagnoses within the 12 months before the index date were excluded, as were those diagnosed with COVID-19 either before the index date or during the follow-up period.

Vaccinated patients were matched to unvaccinated individuals on the basis of greedy nearest-neighbour propensity scores derived from the logistic regression analysis using age, sex, index month (April, May, and June), and diagnoses that may be associated with an increased incidence of thrombosis documented within 12 months before the index date, including obesity (CD-10: E66), atrial fibrillation (ICD-10: I48.0, I48.1, I48.2, I48.9), heart failure (ICD-10: I50), ischaemic heart diseases (ICD-10: I20–I25), cancer (ICD-10: C00–C97), coagulation defects (ICD-10: D65–D69), varicose (ICD-10: I83–I85), injuries (ICD-10: S00–T12, within 6 months) and status postsurgery (ICD-10: Z98, within 6 months). As only vaccination information from GPs and not from vaccination centres was available, unvaccinated individuals (the matched cohort) were selected based on a randomly selected visit date between April and June 2020 because no COVID-19 vaccinations were available during this period (Fig. 1).

### Study outcomes and statistical analyses

The main outcome of the study was the incidence of thrombosis (ICD-10: I80–I82) and non-fatal pulmonary embolism (ICD-10: I26) diagnoses as a function of COVID-19 vaccination. Each individual was followed up for a maximum of 122 days after the index date. Differences in the sample characteristics between vaccinated and unvaccinated individuals were analysed using McNemar tests for categorical variables and paired sample Wilcoxon tests for continuous variables. Poisson regression models were used to obtain incidence rate ratios (IRRs), taking account of differential exposure times via offsets. Marginal models were estimated using the generalised estimation equations method to account for the correlation of observations within matched pairs. *P* values  $< 0.05$  were considered statistically significant. Analyses were carried out using SAS version 9.4 (SAS Institute, Cary, USA).

## Results

### Basic characteristics of the study sample

The present study included 326,833 individuals who received a COVID-19 vaccination between April and June 2021, and 326,833 individuals with a GP visit between April and June 2020. The basic characteristics of the study participants are shown in Table 1. The mean age of participants was 55.7 (standard deviation [SD] 17.3) years; 49.3% were women in both groups. On average, vaccinated individuals were followed up for 38 days and unvaccinated individuals for 34 days after the index date.

### Association between COVID-19 vaccination and thrombosis or non-fatal pulmonary embolism

During the follow-up period, 406 vaccinated patients and 342 unvaccinated patients were diagnosed with thrombosis or non-fatal pulmonary embolism. This resulted in an incidence rate of 11.9 vs 11.3 cases per 1000 patient-years for vaccinated vs unvaccinated individuals, respectively, and a non-significant IRR of 1.06 (95% confidence interval [CI]: 0.93–1.22; see Table 2). The highest IRR was observed in the 41–60 years age group (IRR: 1.30; 95% CI: 0.98–1.73), and the lowest IRR was seen in the 18–40 years age group (IRR: 0.6; 95% CI: 0.0–1.05); however, none of the individual age group incident rates was significant.

## Discussion

Using a large-scale database, this study found no significant difference in the incidence rates of thrombosis or non-fatal pulmonary embolism between individuals who had received the COVID-19 vaccine and matched unvaccinated individuals. In the subgroup of vaccinated individuals aged 41–60 years, the incidence rate of 12.0 cases per 1000 patient-years for thrombosis or non-fatal pulmonary embolism exceeded the value calculated for unvaccinated patients, resulting in an IRR of 1.30. Although this result is non-significant, it must be acknowledged and verified in further investigations. No relevant differences were noted in the other age groups, and no sex-specific trends were detected.

Pivotal trials for SARS-CoV-2 vaccines clearly demonstrate that the vaccines offer great efficacy in preventing severe outcomes of COVID-19.<sup>22–25</sup> In terms of safety, very few severe adverse events related to COVID-19 vaccination have been reported.<sup>22–25</sup> Of the few severe events reported, the most noteworthy are several cases of peripheral facial nerve palsy, one case of transverse myelitis tinnitus, and a number of cases of tinnitus.<sup>22–25</sup> Reports of these uncommon and unexpected severe adverse events remain

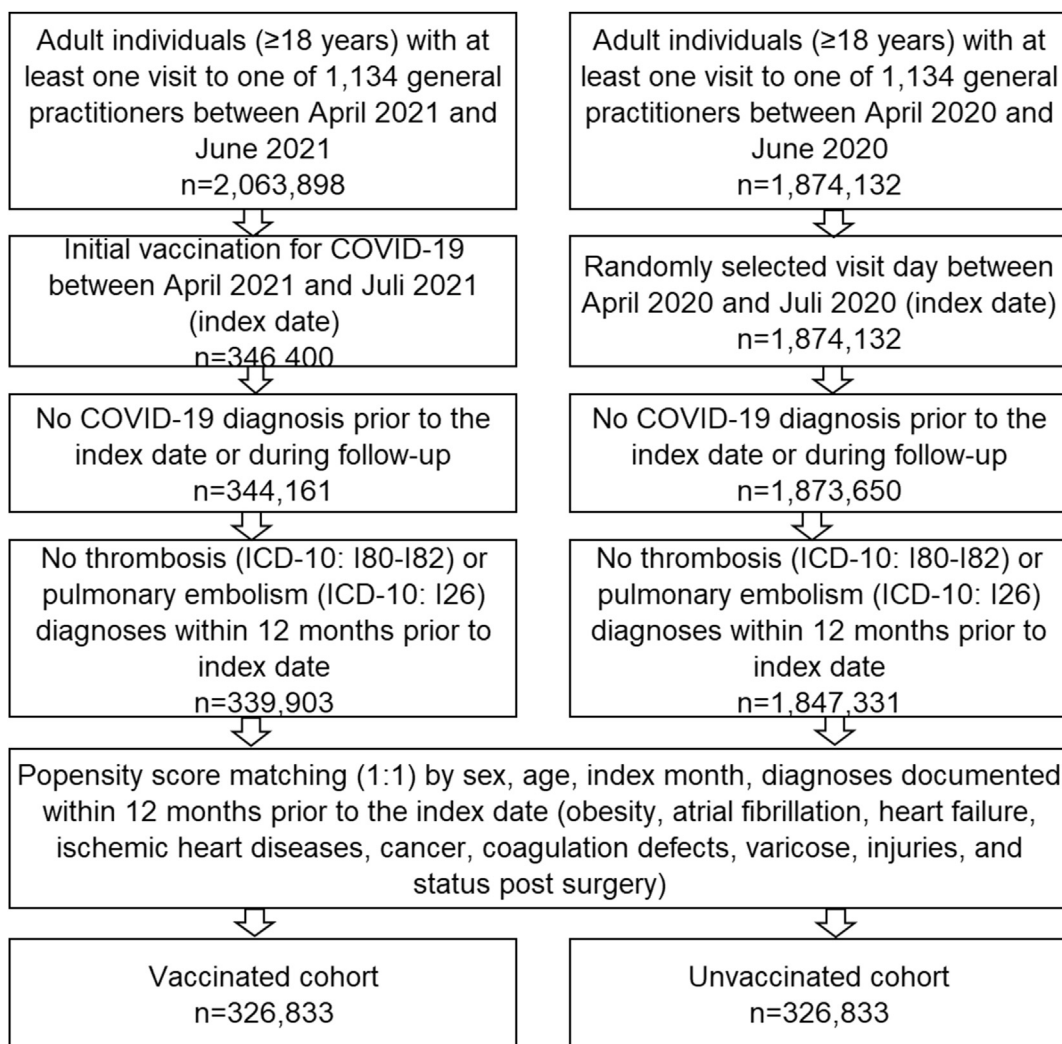


Fig. 1. Selection of study participants.

anecdotal and only involve approximately two dozen individuals across all trials; however, the authors have critically discussed their potential association with the vaccine.<sup>22–25</sup> Among 19,630 individuals receiving a single dose of the Ad26.COV2.S vaccine (Janssen vaccine), 15 cases of thromboembolic events were reported.<sup>24</sup> This number matched rates seen in the placebo group (n = 10), rendering a causative relationship to the vaccination unlikely.<sup>24</sup> However, cases of thrombotic and embolic events were increasingly reported with growing vaccination rates worldwide.<sup>11–15</sup> In November 2021, Bilotta et al. described 58 cases of haemostatic complications after COVID-19 vaccination, demonstrating that both the arterial and venous systems can be affected and identifying cerebral vein thrombosis as the most common event.<sup>12</sup> In a recently published (December 2021) systematic review including 98 studies, Al-Ali et al. described 460 thrombotic events as a potential post-COVID-19 vaccination complication, reporting 159 (34.6%) cases of cerebral vein thrombosis, followed by 67 venous thromboses (14.6%) and 63 cases (13.7%) of pulmonary embolism.<sup>11</sup> Thrombocytopenia was frequently observed in patients with postvaccination thrombotic events, indicating that this phenomenon may be related to the still unclear pathological mechanism behind this adverse reaction.<sup>11–15</sup> However, the data presented on thrombotic and thromboembolic events after COVID-19 vaccination, such as thromboses or pulmonary embolism, are

limited to anecdotal reports or case series. There is currently a lack of data on incidence rates for these events in vaccinated individuals compared with unvaccinated individuals to enable risk estimation.

Vein thrombosis and pulmonary embolism occur frequently in patients with predisposing risk factors. Furthermore, the intake of haemostasis-modulating drugs influences the occurrence of these events.<sup>25,26</sup> The overall crude incidence rate of thrombotic and thromboembolic events in total population is far lower, at around one in 1,000 per year, compared to people with risk factors.<sup>27</sup> The present study participants (vaccinated and matched unvaccinated individuals) may have a low to medium risk of thrombotic and thromboembolic events due to selection bias when prioritising ill or vulnerable individuals for vaccination. However, we detected the same incidence rate in both the vaccinated and unvaccinated groups, which is a major finding of the present study. The incidences of thrombotic and thromboembolic events in the vaccination group detected in the present study represent the expected intrinsic rate in a low- to medium-risk population rather than a result of COVID-19 vaccination. However, although the results of the present study clearly indicate that vaccination against COVID-19 is not a factor for facilitating thrombotic and thromboembolic events, these findings require verification in further large-scale investigations.

**Table 1**  
Basic characteristics of the study participants after 1:1 matching.

Variable	Vaccinated individuals (%) (n = 326,833)	Unvaccinated individuals (%) (n = 326,833)	P-value
Age (mean, SD)	55.7 (17.3)	55.7 (17.3)	0.886
<b>Age group</b>			
18–40 years	20.9	20.9	0.992
41–60 years	35.3	35.3	
61–70 years	24.1	24.1	
>70 years	19.7	19.7	
<b>Sex</b>			
Female	49.3	49.3	1.000
Male	50.7	50.7	
<b>Index month</b>			
April	32.5	32.5	1.000
May	39.5	39.5	
June	28.0	28.0	
<b>Diagnoses in previous 12 months</b>			
Obesity	12.4	12.4	1.000
Atrial fibrillation	4.3	4.3	1.000
Heart failure	4.4	4.4	1.000
Ischaemic heart diseases	9.2	9.2	1.000
Cancer	6.7	6.7	1.000
Coagulation defects	1.0	1.0	1.000
Varicose	5.4	5.4	1.000
Injuries (within last 6 months)	4.0	4.0	1.000
Surgery (within last 6 months)	0.4	0.4	1.000

SD, standard deviation.

Proportions of patients are given in percentage unless otherwise indicated.

**Table 2**  
Association between COVID-19 vaccinations and the incidence of thrombosis or non-fatal pulmonary embolism in patients followed up in general practices in Germany (Poisson regression models).

Variable	Cases per 1000 patient-years among vaccinated individuals	Cases per 1000 patient-years among unvaccinated individuals	IRR (95% CI)	P-value
Total	11.9	11.3	1.06 (0.93–1.22)	0.457
<b>Age group</b>				
18–40 years	4.2	7.4	0.56 (0.30–1.05)	0.072
41–60 years	12.0	9.2	1.30 (0.98–1.73)	0.067
61–70 years	11.6	11.3	1.03 (0.78–1.35)	0.828
>70 years	14.9	14.5	1.03 (0.82–1.29)	0.784
<b>Sex</b>				
Female	12.6	12.5	1.02 (0.84–1.23)	0.879
Male	11.1	10.0	1.12 (0.90–1.38)	0.339

CI, confidence interval; IRR, incident rate ratio.

The two major strengths of this study are the number of patients available for analysis and the detailed analyses performed using real-world data. This study is also subject to several limitations that should be acknowledged. First, the thrombosis and pulmonary embolism diagnosis data relied solely on ICD-10 codes, and no data were available on the diagnosis process or the severity/activity of the disease. Second, as no information was available on behavioural factors (e.g. alcohol use, smoking, use of contraceptive drugs and sedentary lifestyle), the roles played by these factors could not be examined. Third, no hospital data were available, and only out-patients were analysed; severe cases of both COVID-19 and thrombosis are treated in hospitals. Fourth, analyses were not stratified by vaccination manufacturer; however, >90% of patients in this study received the BNT162b2 vaccine, a COVID-19 messenger RNA vaccine. Fifth, injuries as a risk factor for thromboses was not included in the match-pairs variables because of the very small number of individuals with documented injuries during the study period. Finally, the database does not contain data on mortality; thus, no fatal events could be analysed.

### Conclusions

In this large-scale investigation examining the incidences of thrombosis and pulmonary embolism, no differences were detected

between COVID-19-vaccinated and unvaccinated individuals. It is therefore very likely that when these conditions occur after SARS-CoV-2 vaccination, they are an inevitable part of the medical history of the individual rather than a consequence of vaccination.

### Author statements

#### Ethical approval

The database used in this study includes only anonymised data in compliance with the regulations of the applicable data protection laws. German law allows the use of anonymous electronic medical records for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for this type of observational study that contains no directly identifiable data. As patients were only queried as aggregates and no protected health information was available for queries, no institutional review board approval was required for the use of this database or the completion of this study.

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## Competing interests

All authors hereby declare that they have no conflicts of interest or competing interests related to the current article.

## Author contributions

KK and CT developed the idea for the study, KK and RZ analyzed the data. CT, JR and KK wrote the manuscript. All authors contributed to and reviewed the final version of the manuscript.

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