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Infectious Disease Practice

Likelihood of Post-COVID Condition in people with hybrid immunity; data from the German National Cohort (NAKO)

Rafael Mikolajczyk [a,*,1], Sophie Diexer [a,1], Bianca Klee [a], Laura Pfrommer [a], Oliver Purschke [a], Julia Fricke [b], Peter Ahnert [c], Sabine Gabrysch [d,e,f], Cornelia Gottschick [a], Barbara Bohn [g], Hermann Brenner [h], Christoph Buck [i], Stefanie Castell [j], Sylvia Gastell [k], Karin Halina Greiser [l], Volker Harth [m], Jana-Kristin Heise [j], Bernd Holleczek [n], Rudolf Kaaks [l], Thomas Keil [b,o,p], Lilian Krist [b], Michael Leitzmann [q], Wolfgang Lieb [r], Claudia Meinke-Franze [s], Karin B. Michels [t], Ilais Moreno Velásquez [u], Nadia Obi [m], Leo Panreck [g], Annette Peters [v,w], Tobias Pischon [u], Tamara Schikowski [x], Börge Schmidt [y], Marie Standl [v,z], Andreas Stang [y], Henry Völzke [s], Andrea Weber [q], Hajo Zeeb [i,aa], André Karch [ab]

[a] Institute for Medical Epidemiology, Biometrics, and Informatics, Interdisciplinary Centre for Health Sciences, Medical Faculty of the Martin Luther University Halle-Wittenberg, Halle (Saale), Germany
[b] Institute of Social Medicine, Epidemiology and Health Economics, Charité – Universitätsmedizin Berlin, Berlin, Germany
[c] Institute for Medical Informatics, Statistics and Epidemiology, Universität Leipzig, Leipzig, Germany
[d] Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute of Public Health, Berlin, Germany
[e] Research Department 2, Potsdam Institute for Climate Impact Research (PIK), Member of the Leibniz Association, Potsdam, Germany
[f] Heidelberg Institute of Global Health, Heidelberg University, Heidelberg, Germany
[g] NAKO e.V., Heidelberg, Germany
[h] Division of Clinical Epidemiology and Aging Research, German Cancer Research Centre (DKFZ), Heidelberg, Germany
[i] Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany
[j] Department for Epidemiology, Helmholtz Centre for Infection Research, Braunschweig, Germany
[k] NAKO Study Centre, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany
[l] Division of Cancer Epidemiology, DKFZ Heidelberg, Heidelberg, Germany
[m] Institute for Occupational and Maritime Medicine Hamburg (ZfAM), University Medical Centre Hamburg-Eppendorf (UKE), Hamburg, Germany
[n] Krebsregister Saarland, Saarbrücken, Germany
[o] Institute of Clinical Epidemiology and Biometry, University of Würzburg, Würzburg, Germany
[p] State Institute of Health I, Bavarian Health and Food Safety Authority, Erlangen, Germany
[q] Institute of Epidemiology and Preventive Medicine, Regensburg, Germany
[r] Institute of Epidemiology, Kiel University, Kiel, Germany
[s] Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany
[t] Institute for Prevention and Cancer Epidemiology, Faculty of Medicine and Medical Centre, University of Freiburg, Freiburg, Germany
[u] Max-Delbrueck-Center for Molecular Medicine in the Helmholtz Association (MDC), Molecular Epidemiology Research Group, Berlin, Germany
[v] Institute of Epidemiology, Helmholtz Zentrum München - German Research Centre for Environmental Health (GmbH), Neuherberg, Germany
[w] Chair of Epidemiology, Institute for Medical Information Processing, Biometry and Epidemiology, Medical Faculty, Ludwig-Maximilians-Universität München, Munich, Germany
[x] IUF-Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany
[y] Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Essen, Germany
[z] German Centre for Lung Research (DZL), Munich, Germany
[aa] Health Sciences Bremen, University of Bremen, Bremen, Germany
[ab] Institute of Epidemiology and Social Medicine, University of Münster, Münster, Germany

* Correspondence to: Institute for Medical Epidemiology, Biometrics, and Informatics, Interdisciplinary Centre for Health Sciences, Medical Faculty of the Martin Luther University Halle-Wittenberg, Magdeburger Str. 8, 06112 Halle (Saale), Germany.
E-mail address: rafael.mikolajczyk@uk-halle.de (R. Mikolajczyk).
[1] These authors contributed equally.

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SUMMARY

Objectives: The risk of Post-COVID-19 condition (PCC) under hybrid immunity remains unclear.
Methods: Using data from the German National Cohort (NAKO Gesundheitsstudie), we investigated risk factors for self-reported post-infection symptoms (any PCC is defined as having at least one symptom, and high symptom burden PCC as having nine or more symptoms).
Results: Sixty percent of 109,707 participants reported at least one previous SARS-CoV-2 infection; 35% reported having had any symptoms 4–12 months after infection; among them 23% reported nine or more symptoms. Individuals, who did not develop PCC after their first infection, had a strongly reduced risk for PCC after their second infection (50%) and a temporary risk reduction, which waned over 9 months after the preceding infection. The risk of developing PCC strongly depended on the virus variant. Within variants, there was no effect of the number of preceding vaccinations, apart from a strong protection by the fourth vaccination compared to three vaccinations for the Omicron variant (odds ratio = 0.52; 95% confidence interval 0.45–0.61).
Conclusions: Previous infections without PCC and a fourth vaccination were associated with a lower risk of PCC after a new infection, indicating diminished risk under hybrid immunity. The two components of risk reduction after a preceding infection suggest different immunological mechanisms.

Introduction

Following cases of post-acute infection syndrome during the early stages of the COVID-19 pandemic, the World Health Organization (WHO) has defined post-COVID-19 condition (PCC) as new or persistent symptoms that occur 12 weeks after a SARS-CoV-2 infection and cannot be explained by other causes.[1] It has been estimated that approximately 65 million people worldwide have been affected by PCC by 2023.[2] Although PCC has been reported to be more common after a severe infection,[3,4] it can also occur after a mild infection that does not require hospitalization.[5]

Previous studies indicated that the risk of developing PCC was higher for the early virus variants than for the Omicron variant.[3,6–8] In case PCC occurred, similar PCC symptom profiles were observed for the different variants.[8,9] Vaccination reduces the risk of symptomatic infection and severe COVID-19,[10,11] and thus indirectly also the risk of PCC, postulated effects regarding the relationship between previous vaccinations and PCC development in breakthrough infections vary.[8,9,12] Furthermore, a substantially reduced PCC risk has been reported for individuals after the second SARS-CoV-2 infection (among those, who had not developed PCC after their first infection) compared to individuals after the first SARS-Cov-2 infection.[8]

In 2023, the COVID-19 pandemic was officially declared over,[13] and SARS-CoV-2 infections are now considered part of an ongoing endemic phase. As the protection offered by vaccines and previous infections against (re)infection with the Omicron variant is only partial and temporary, and non-pharmaceutical measures like masks are unlikely to be applied on a population level, large parts of the population likely experience repeated infections over the next few years.[14] Some authors predicted a substantial burden of PCC,[15] while others suggested that an increased risk will only be present during a transition period.[8] Most of the unsolved questions around PCC risk affect the development of PCC after repeated infections and under conditions of hybrid immunity, i.e., in individuals who had preceding infections and vaccinations. Since systematic testing for SARS-CoV-2 infection is unlikely to continue in the future, data from the pandemic period, which included widely available testing even for mild cases, provides a unique opportunity to study the risk of PCC under the conditions of hybrid immunity.

The objective of this study was to evaluate the impact of preceding vaccinations and SARS-CoV-2 infections on the risk of developing PCC after a subsequent infection, taking into account the SARS-CoV-2 variant and the time since the previous infection or vaccination.

Methods

Study population

We used data from the German National Cohort (NAKO; NAKO Gesundheitsstudie). The study is described in detail elsewhere.[16] In brief, 205,415 individuals between 20–69 years old, who were randomly selected from registration offices, were recruited between 2014 and 2019. They were examined in 18 study centres across Germany. These participants are currently undergoing their second examination, 5 years after the baseline examination. In addition to these on-site examinations, NAKO conducted an online survey between September and December 2022 focusing on SARS-CoV-2 infections and symptoms potentially linked to PCC. 150,722 participants with valid email addresses were invited to participate in this survey, of which 110,375 (73.2%) completed it. Of these, 668 cases were excluded due to incomplete information on dates of vaccination or contradictory reports regarding timing of vaccinations.

Definition of exposure, outcome and covariables

The online questionnaire collected information about general health and current symptoms potentially related to PCC. It also collected retrospective information about number and timing of vaccinations, SARS-CoV-2 infections (dates of vaccination and infections were reported as month/year), and symptoms for four time periods after the first and last infection. These time periods included the time during the acute infection, 2 to 3 months after infection, 4 to 12 months, and 1 year or more after infection. The symptom list was developed based on previous research and included 21 symptoms. For acute infection, we asked about each of the symptoms individually. For the other three periods, we first asked if the participant experienced any of the following symptoms (all symptoms were listed) and if the response was “yes”, the participants were asked for each specific symptom whether or not they had experienced it.

For the purposes of this study, we defined “any PCC” if the response was “yes” to the first question regarding presence of any symptoms for the time window 4 to 12 months after a SARS-CoV-2 infection. We also applied an additional, more restrictive definition of “high symptom burden PCC” including only those with 9 symptoms or more. We classified virus variants responsible for a given infection according to the periods of dominance of the specific variant in the national surveillance data in Germany.[17] Infections before

January 2021 were categorised as Wildtype, those between January and June 2021 as Alpha variant, those between July and December 2021 as Delta variant, and infections from January 2022 as Omicron variant. We performed a sensitivity analysis that excluded transition periods between dominant variants. The transition periods were defined as the interval 1 month before and after the cut-off dates. Two infections had to be more than 3 months apart, to be considered as reinfections.

Data analysis

We report frequencies and percentages as descriptive statistics. After a general description, the sample was restricted to those who reported no infection or whose infection was at least 4 months ago, allowing for symptom reporting within the 4–12 month time window. In the main analysis, we evaluated how the risk of any PCC and high symptom burden PCC was associated with virus variants and the number of vaccinations and infections preceding the respective infection, using analyses stratified by virus variant. We reported frequencies and risk differences compared to the risk of PCC after the Wildtype virus variant. In the next step, we restricted the sample only to persons with vaccinations, due to a strong collinearity between virus variants and vaccinations, and analysed associations of sociodemographic variables, time since last vaccination, time since last infection, and virus variant with the risk of developing self-reported and high symptom burden PCC (in separate analyses) using multivariable logistic regression models. Each individual is included only once. This means that those with two infections are only analysed for the second infection, in case they did not develop PCC at their first infection. We conducted multiple sensitivity analyses, excluding periods in which the dominance of virus variants changed. Additionally, we assessed the effect of four vaccinations in comparison to three on the risk of PCC. This analysis was restricted on the Omicron variant. In another sensitivity analysis, we assessed whether the effects of vaccinations and preceding infections are independent by analysing only the first infection of the infected individuals. We stratified the analysis by sex and age groups. Time components of protection after preceding infection were visualised using generalised additive models as implemented in the mgcv[18] and segmented[19] package in R. We used R 4.2.0 for all analyses.

Results

Characteristics of the participants

Of the 109,707 NAKO participants analysed, almost 60% reported a previous SARS-CoV-2 infection (Table 1). The majority of those infected (> 90%) experienced only one infection. More than 80% of the participants had received three or more COVID-19 vaccinations. Of those infected, 84% did not receive medical treatment and less than 1% were hospitalized during the acute infection.

Among the respondents who were infected and observed for at least 4 months after infection, 35% reported experiencing symptoms in the time window of 4 to 12 months after a SARS-CoV-2 infection. Out of the 19,476 individuals who reported symptoms during this time window, 4525 (23%) had nine or more symptoms, and were classified as a high symptom burden PCC.

Influence of virus variant, previous infections and vaccinations

In analyses stratified by three factors: virus variant, having a previous infection, and number of preceding vaccinations, any PCC occurred in around 7% after an infection during the Omicron phase for those with a previous infection and in 47% after initial infection with the Wildtype virus (Table 2). Individuals who had a previous infection and did not develop any PCC had a lower risk of developing PCC after the second infection compared to those with no preceding infection (Table 2 and Fig. S1). When comparing participants with varying number of vaccinations for a specific virus variant, we found a better protection against any PCC only in case of a breakthrough

Table 1
Description of the study population (N = 109,707).

	All		At least one previous infection	
Characteristic	N	%	N	%
Total	109,707		65,773	
Sex				
Male	53,563	48.8%	31,709	48.2%
Female	56,144	51.2%	34,064	51.8%
Age group				
20–29	3315	3.0%	2499	3.8%
30–39	13,040	11.9%	9512	14.5%
40–49	18,207	16.6%	12,781	19.4%
50–59	34,398	31.4%	21,596	32.8%
60–69	26,261	23.9%	13,387	20.4%
70+	14,486	13.2%	5998	9.1%
Study centre				
Augsburg	10,899	9.9%	6836	10.4%
Regensburg	5515	5.0%	3493	5.3%
Mannheim	5960	5.4%	3571	5.4%
Freiburg	6876	6.3%	4254	6.5%
Saarbrücken	5540	5.0%	3264	5.0%
Essen	5613	5.1%	3270	5.0%
Münster	5728	5.2%	3431	5.2%
Düsseldorf	4698	4.3%	2845	4.3%
Halle	4859	4.4%	2943	4.5%
Leipzig	5271	4.8%	3220	4.9%
Berlin Nord	6428	5.9%	3780	5.7%
Berlin Mitte	6614	6.0%	4003	6.1%
Berlin Süd	6085	5.5%	3641	5.5%
Hannover	4426	4.0%	2516	3.8%
Hamburg	6193	5.6%	3671	5.6%
Bremen	6517	5.9%	3618	5.5%
Kiel	4709	4.3%	2667	4.1%
Neubrandenburg	7776	7.1%	4750	7.2%
Number of reported SARS-CoV-2 infections				
None	43,934	40.0%	-	-
1	60,152	54.8%	60,152	91.5%
2	5383	4.9%	5383	8.2%
3	208	0.2%	208	0.3%
4	30	< 0.1%	30	< 0.1%
Number of reported vaccinations[a]				
None	4213	3.8%	2987	4.5%
1	991	0.9%	880	1.3%
2	9614	8.8%	7462	11.3%
3	72,407	66.0%	45,906	69.8%
4	19,614	17.9%	7094	10.8%
I do not want to report it	1252	1.1%	791	1.2%
Missing	1616	1.5%	653	1.0%
Any PCC				
Yes	19,476	17.8%	19,476	29.6%
No	35,271	32.2%	35,271	53.6%
Never infected	43,934	40.0%	0	0.0%
Not possible to determine[b]	10,690	9.7%	10,690	16.3%
Missing	336	0.3%	336	0.5%
Number of symptoms during acute infection[c]				
0–2			8701	13.2%
3–5			12,522	19.0%
6–8			17,116	26.0%
9 or more			27,434	41.7%

PCC = Post-COVID condition.
[a] Irrespective of whether before or after infection leading to PCC.
[b] Infection within 3 months before administration of the questionnaire (therefore no classification regarding PCC possible).
[c] Refers to infection leading to PCC for those who developed PCC and to first infection for those who did not develop PCC. In the following analyses, individuals with more than two infections were excluded.

Table 2
Preceding exposures and the risk of developing Post-COVID Condition (PCC)[a].

Variant	Number of vaccinations[b]	N infected	% any PCC	% high symptom burden PCC
Only first infection (N = 54,512)				
Wildtype	0	3876	46.78%	11.30%
Alpha	0	2835	41.94%	11.01%
Alpha	1–2	411	33.09%	8.52%
Delta	0	1206	37.56%	9.87%
Delta	1–2	2671	39.99%	9.51%
Delta	3	107	45.79%	9.35%
Omicron	0	5088	29.54%	7.90%
Omicron	1–2	7942	33.03%	8.16%
Omicron	3	29,249	34.32%	7.45%
Omicron	4	1127	23.51%	4.88%
Only second infection of individuals who did not develop PCC after their first infection (N = 2611)				
Alpha	0	91	8.79%	1.10%
Alpha	1–2	23	4.35%	< 0.01%
Delta	0	62	3.23%	< 0.01%
Delta	1–2	78	2.56%	< 0.01%
Delta	3	3	< 0.01%	< 0.01%
Omicron	0	469	6.61%	1.07%
Omicron	1–2	1075	7.16%	0.93%
Omicron	3	784	8.67%	0.89%
Omicron	4	26	3.85%	< 0.01%

PCC = Post-COVID condition.
[a] Only individuals with one or two infections, and whose infection was more than 3 months before administering the questionnaire, so that presence of symptoms after 3 months could be assessed.
[b] Number of vaccinations preceding infection resulting in PCC.

infection after four vaccinations for Omicron or one to two vaccinations for the Alpha variant compared to the corresponding groups with fewer vaccinations (Table 2 and Fig. S1).

In the multivariable model that only includes vaccinated individuals, there was evidence of an association between the risk of any PCC and the time since the preceding infection and the time since the last vaccination, after adjusting for age, sex, study centre, and the number of symptoms during acute infection (Table 3). As demonstrated in the stratified analysis, the risk of developing any PCC after the second infection (in those who did not develop it after their first infection) was substantially lower compared to after the first infection, resulting in a long-term risk reduction of around 50%. There was an additional temporary risk reduction, which waned over time in 9 months after the preceding infection (max. 50% reduction relative to the long-term effect) (Fig. 1a and b). Only 30 cases of high symptom burden PCC occurred in individuals who had a second infection after a previous infection without high symptom burden PCC. Therefore, it was not possible to conduct an analysis of the effect of time on the high symptom burden PCC.

In contrast, the risk of developing PCC after an infection was higher when infections occurred within the first 3 months after receiving a SARS-CoV-2 vaccination. This risk was higher by approximately 50% compared to infections that occurred between 4 to 6 months or longer after the last vaccination (Table 3). The same results were obtained when a more restrictive definition of variant dominance was used, which excluded transition periods (Table S1). The mutually adjusted results for time since last vaccination and previous infection/time since last infection were similar to analyses based only on the first infection (Table S2). All effect sizes were similar for the endpoints of any PCC and high symptom burden PCC. Results of the analyses stratified by sex and age did not show evidence for any effect modification (Table S4).

The subsample with four vaccinations was small, and models including and excluding this group produced virtually the same results (Table S5 compared to Table 3). Therefore, we separately studied the effect of four vaccinations versus three vaccinations in a multivariable model for the Omicron variant only and found a substantial risk reduction (odds ratio = 0.52, 95% confidence interval 0.45–0.61) (Table S6).

Discussion

Our findings indicate that the risk of developing PCC was strongly reduced for the second SARS-CoV-2 infection, if the first infection did not result in PCC. The risk reduction consisted of two components: a persistent, time-independent risk reduction and an additional risk reduction for reinfections that occurred shortly after a previous infection. The latter diminished over the first 9 months. In addition, we found a substantial risk reduction after the fourth vaccination in comparison to three or fewer vaccinations prior to an infection during the Omicron dominance period, otherwise vaccinations did not offer direct protection. However, we also found a period of increased vulnerability towards PCC when a breakthrough SARS-CoV-2 infection occurred within 0 to 3 months of vaccination. We confirmed previous studies reporting differences in the risk of developing PCC across virus variants responsible for the infection.

Consistent with a previous study,[8] we found that experiencing a previous infection without developing PCC is associated with a substantially reduced risk of PCC after a second infection. Taking advantage of the large sample size in our study, we could identify two factors contributing to this reduction: a protection that begins after an infection and decreases over 9 months, as well as a consistently lower risk thereafter. The first component suggests a correlation with immunity, with decreasing levels of protection over time. The absence of this effect following vaccination may indicate a difference in the immunological response between vaccination and infection, possibly with a stronger role of the cellular component in the latter. Due to the small number of affected individuals, we were unable to evaluate this component in the analysis limited to high symptom burden PCC. The second, long-term component can be of cellular nature or possibly indicate that not having developed PCC after the first infection is an indicator of some natural predisposition. More research on mechanisms of infection and immunity and their role in the development of PCC on the one side and possible predisposition on the other side is needed to clarify this issue.

According to a recent meta-analysis, vaccination provides protection against PCC.[4] However, other studies have reported a lack of protective effect against PCC after a breakthrough infection.[7,8,20] This disagreement may be due to the fact that early studies used definitions of PCC based on shorter follow-up periods after infection, during which signs of acute infection may still be present.[12] Recent studies suggest that the previously observed protective effects of vaccination disappear when adjusting for virus variants in the analysis. It is important to note that vaccination status differs by variant, and not considering variants can falsely attribute the lower risk of PCC for the newer variants to the higher prevalence of vaccination.[8,20] At the same time, we demonstrated a protection provided by the fourth vaccination for the Omicron variant. Given the time when the fourth vaccination was available, we have to assume that the vaccine used in our sample was not yet tailored to the Omicron variant. A recent analysis reported increased protection offered by three vaccinations when compared to two for the Omicron variant.[21] While there was some indication of this difference in our data, we could not replicate it, but instead observed a difference for the fourth vaccination compared to the third. For the third vaccination (first booster), it was observed that the immunological response was broader.[22] Therefore, it is plausible that better protection can be achieved with each new vaccination. At the same time, given that more preceding vaccinations were not protective at earlier stages, we cannot exclude that the observed effect is a consequence of some yet unknown mechanism of bias, for example a decreasing awareness towards symptoms of PCC in the final stages of the pandemic.

Table 3
Variables associated with the risk of developing post-COVID condition (PCC) restricted to individuals with at least one vaccination (N = 42,036)[a] (multivariable analysis).

			Any PCC		High symptom burden PCC	
		N	aOR	95% CI	aOR	95% CI
Sex	Male	20,515	Ref.		Ref.	
	Female	21,521	1.37	1.31; 1.43	1.78	1.63; 1.93
Age group	20–29	1851	Ref.		Ref.	
	30–39	6458	1.22	1.09; 1.38	1.15	0.93; 1.43
	40–49	8538	1.44	1.28; 1.61	1.41	1.14; 1.73
	50–59	13,692	1.39	1.24; 1.55	1.54	1.26; 1.88
	60–69	8066	1.30	1.16; 1.46	1.40	1.13; 1.73
	70+	3431	1.18	1.03; 1.34	1.31	1.02; 1.69
Variant[b]	Omicron	39,178	Ref.		Ref.	
	Delta	2494	1.40	1.28; 1.53	1.21	1.04; 1.41
	Alpha	364	0.76	0.60; 0.97	1.09	0.73; 1.62
Months since last vaccination	0–3	21,107	1.57	1.50; 1.65	1.56	1.43; 1.70
	4–6	16,115	Ref		Ref	
	7–9	3408	0.89	0.82; 0.97	1.06	0.91; 1.24
	10–12	941	1.10	0.94; 1.28	1.07	0.89; 1.41
	13 or more	465	0.73	0.58; 0.91	0.79	0.51; 1.23
Months since last infection	No previous infection	40,682	Ref.		Ref.	
	4–6	420	0.34	0.24; 0.47	0.55	0.27; 1.13
	7–9	98	0.55	0.32; 0.96	0.37	0.09; 1.57
	10–12	103	0.36	0.19; 0.67	0.53	0.13; 2.21
	13–18	369	0.49	0.36; 0.66	0.48	0.22; 1.02
	19–24	196	0.41	0.27; 0.63	0.34	0.11; 1.07
	25 or more	168	0.51	0.34; 0.78	0.48	0.17; 1.33
Number of symptoms during acute infection	0–2	6362	Ref.		Ref.	
	3–5	8767	1.67	1.53; 1.83	1.16	0.85; 1.60
	6–8	11,248	2.60	2.39; 2.82	2.56	1.94; 3.37
	9 or more	15,659	5.79	5.35; 6.26	18.43	14.30; 23.73

PCC = Post-COVID condition. Ref = reference. aOR = adjusted odds ratio (adjusted for all variables in the table and additionally adjusted for study center). CI = Confidence Interval.
[a] Only vaccinated individuals with one or two SARS-CoV-2 infections and whose infection was more than 3 months before administering the questionnaire, so that presence of symptoms after 3 months could be assessed.
[b] Refers to infection which led to PCC among those who developed PCC and to the infection being compared to (i.e. either first or second).

Vaccination protects against symptomatic infection and severe COVID-19[10,11] and therefore indirectly reduces the risk of PCC. The reported lack of protection by vaccination in the current study only refers to the direct effect, i.e. the effect independent of protection against infection and the reduced severity of acute infection. Our results indicate that there is no general protective effect resulting from vaccination after the acute infection has been dealt with. This suggests that immunological reactions related to vaccination, such as titre increase as a protective mechanism, are not linked to PCC. These findings have implications for the understanding of the role of immunological mechanisms in PCC.

We found some evidence of an increased risk of PCC following an infection shortly after vaccination, which has not been previously reported in the literature. This finding may be explained by the fact that the vaccination had not yet built up a protective response against more severe acute infection, leading to a lack of indirect protection and falsely attributing an increased risk of PCC to the time period following vaccination. Therefore, we repeated the analysis presented in Table 3 without adjusting for symptoms of acute infection (Table S3). This adjustment attenuated the observed temporal risk increase, but did not remove it. It is possible that the occurrence of breakthrough infections shortly after vaccination is linked to a specific vulnerability of the individual towards PCC, and the apparent protection actually results from confounding. Studies assessing immunological repertoires before infection can provide further insights; the German National Cohort with its in-depth biobanking is suitable for such analyses.

Several studies proposed that the risk of developing PCC differs across virus variants and is lower for Omicron than for earlier variants.[3,6–9,20,21,23,24] Our results are consistent with these findings. Of particular interest are the very similar results from the online research platform DigiHero, which used a similar questionnaire and data on 17,008 SARS-CoV-2 infections and 2822 PCC cases from Germany.[8]

For most described effects, there was no indication of differences in the results for any PCC and high symptom burden PCC. This supports the notion that PCC is a continuous spectrum of varying severity, often not requiring medical attention, rather than a small group of patients with a “true” PCC in whom symptoms were triggered by the SARS-CoV-2 infection and which is hidden in a large group with symptoms unrelated to the infection (no PCC).

Our analysis has several limitations. Firstly, we employed the WHO definition of PCC, which does not differentiate between the severity or clinical relevance of symptoms. Additionally, the analysis relied on self-reported infections, vaccinations, and symptoms, which may have influenced the findings in various ways. Individuals with SARS-CoV-2 infections and subsequent symptoms may have been more inclined to participate in this substudy of NAKO than those without. This potentially inflated the estimates of incidence of infection and PCC. Additionally, they may have been more likely to report a wider range of symptoms. On the other side, it is also possible that some individuals did not participate in the substudy due to the severity of their symptoms. The recall periods differed for PCC resulting from different virus variants. Those reporting symptoms after a longer recall time were also more likely to have experienced more persistent and more severe symptoms, aiding their memory. This could have influenced the ratio of mild to high symptom burden cases across the virus variants. Relative estimates, however, were less affected as all components were subject to the same limitations. The data collection was conducted only online, which may have excluded some potential participants. We focussed on the role of virus variants, infections, and vaccinations and did not assess the impact of the pandemic measures[25] and the differential socio-economic burden[26] on the symptoms associated with PCC. Finally, we could not assess the potential effect of treatments of acute infection, as this was not assessed in the questionnaire.

The strength of our study lies in its large population-based sample of individuals recruited for the prospective German National

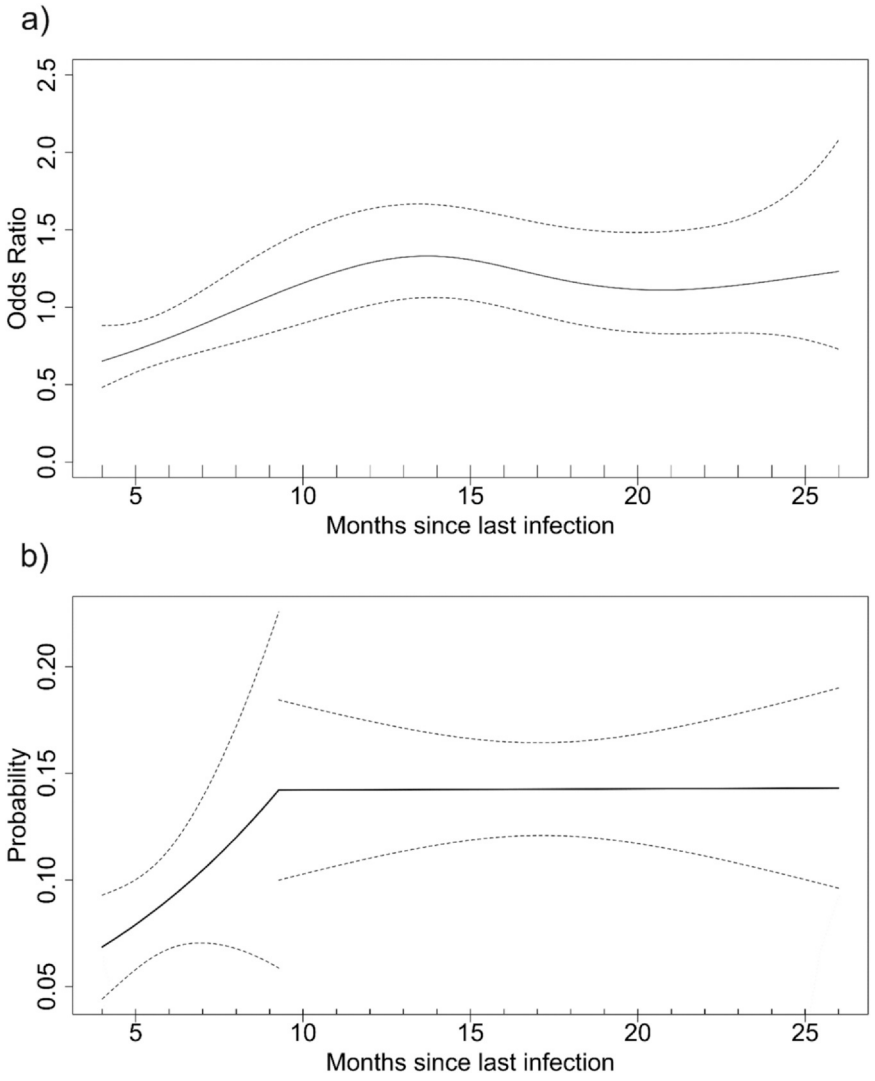

Fig. 1. Association between time since preceding infection and the expected risk of experiencing any PCC after a reinfection (N = 1675), in relation to time since preceding infection: (a) odds ratio relative to a mean effect (generalized additive model using splines as implemented in mgcv package in R, dotted lines indicate 95% confidence intervals), (b) proportion developing PCC (segmented regression as implemented in segmented package in R, dotted lines indicate 95% confidence intervals) (adjusted for sex, age, study centre, variant, and months since last vaccination, and symptoms at acute infection).

Cohort. These individuals are being followed for many years with regular examinations, and a high proportion of those invited to this survey have participated. While other studies on PCC are often based on hospital populations,[3,27] the analysed sample includes mainly individuals with mild infections who have not necessarily been diagnosed with PCC and whose test results have not always been reported to the health authorities. This is particularly relevant for infections caused by the Omicron variant, as reporting during this period was often incomplete. It is important to note that we did not have information on whether our participants received a clinical diagnosis of PCC. The clinical diagnosis of PCC is still not well standardised and while it may be more relevant for severe cases, it likely favours those who were hospitalised during acute infection, as they receive increased medical attention even after leaving the hospital. To supplement our analysis based on at least one symptom (any PCC), which may include very mild cases, we used a more restrictive definition that requires the presence of nine or more symptoms (high symptom burden PCC). This subgroup reported substantially reduced self-reported health. Still, the results were similar, indicating that mild and more severe PCC build a continuum with respect to the studied associations.

In conclusion, our findings suggest that hybrid immunity is likely to considerably decrease the long-term incidence of PCC. More recent virus variants are associated with a lower risk, and individuals who did not develop PCC after a previous infection are less likely to develop it after the next infection. Although we did not find that vaccination offered a general independent protection against PCC, there appears to be a protective effect linked to the fourth vaccination. In addition, vaccinations reduce the risk of PCC by lowering the risk of infection and the severity of the infection.

Ethics approval statement

The NAKO was approved by the ethical review committees of all participating NAKO study centres. Informed consent was obtained from all participants.

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CRediT authorship contribution statement

RM, SD, and AK conceptualised the research question. RM, JF, PA, SG, CG, BB, KHG, LP, TP, and AK designed the study questionnaire. RM, BK, and LPR wrote the original draft of the manuscript. RM, AK, SD, BK and LPR contributed to the literature review. SD and OP performed the data analysis. OP was responsible for data curation. BB, KHG, NO, LP and TP contributed to data collection. AK, SD, JF, PA, SG, CG, BB, HB, CB, SC, SG, KHG, VH, J-KH, BH, RK, TK, LK, ML, WL, CM-F, KBM, IMV, NO, LP, AP, TP, TS, BS, MS, AS, HV, AW, and HZ contributed to reviewing and editing of the manuscript. RM, AK, HB, SC, KHG, VH, J-KH, BH, RK, LK, ML, WL, CM-F, KBM, NO, AP, TP, BS, AS, HV, AW, and HZ provided supervision of the original study. RM and AK provided supervision of the analysis. RM, AK, HB, KHG, VH, BH, RK, TK, ML, WL, KBM, AP, TP, TS, BS, AS and HV were responsible for funding acquisition. RM, SD, and OP directly accessed and verified the underlying data reported in the manuscript. All authors accepted the final version of the manuscript and take responsibility for the decision to submit for publication.

Data availability statement

Data used for this analysis can be made available upon request to the Use and Access Committee of the NAKO. The request can be submitted via: https://transfer.nako.de/transfer/index.

Declaration of Competing Interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106206.

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